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### Chronic kidney disease

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# nature REVIEWS

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## 1 Chronic kidney disease

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## 47 **Abstract**

48 Chronic kidney disease (CKD) is defined by persistent urinary abnormalities or impaired excretory  
49 renal function. While progression to end stage kidney disease (ESKD) is a concern, the majority of  
50 those with CKD are at risk for accelerated cardiovascular disease and death. For those that do reach  
51 ESKD the limited accessibility to kidney replacement therapy is a problem in many locations  
52 worldwide.. Risk factors for CKD include low nephron number at birth and nephron loss due to  
53 increasing age or acute and chronic kidney injuries. For example, the pandemic of obesity and type 2  
54 diabetes largely accounts for the increasing global prevalence of CKD and there is an increasing  
55 awareness of genetic causes for CKD and accelerated CKD progression. The management of CKD is  
56 focused on early detection or prevention, treatment of the root cause if possible, and attention to  
57 secondary processes which contribute to ongoing nephron loss, i.e. remnant nephron hyperfiltration.  
58 Blood pressure control and inhibition of the renin-angiotensin system are the corner stones of  
59 therapy. CKD complications such as CKD complications such as anemia, metabolic acidosis, and  
60 secondary hyperparathyroidism impact cardiovascular health, as well as quality of life, and so require  
61 diagnosis and therapy. Primary prevention of CKD, early diagnosis, and secondary prevention of CKD  
62 progression are needed to reduce cardiovascular disease, CKD-related morbidity, and to prevent  
63 ESKD, whether or not kidney replacement therapies are available.

64

## 65 **[H1] Introduction**

66 Chronic kidney disease (CKD) is a syndrome defined as persistent alterations in kidney  
67 structure, function or both with implications for health <sup>1</sup>. Examples of structural abnormalities  
68 include cysts, tumors, malformations or atrophy, which become evident by imaging. By contrast,  
69 kidney dysfunction can become evident as hypertension, edema, growth delay in children, and  
70 changes in output or quality of urine; these changes are most often recognized by increased serum  
71 levels of creatinine, cystatin C or blood urea nitrogen. The most common pathological manifestation,

72 regardless of the initiating insult or disease, of CKD is some form of renal fibrosis.

73 The Kidney Disease Improving Global Outcomes (KDIGO) initiative classifies an individual as having

74 CKD if abnormalities of kidney structure or function persist for >3 months. KDIGO describes a

75 classification system based on severity, into numerous stages of CKD using a two dimensional matrix

76 based on estimated or measured glomerular filtration rate (eGFR, mGFR) and on extent of

77 albuminuria (FIG. 1)<sup>1</sup>. Primary care settings often do not assess albuminuria but proteinuria via dip

78 stick analysis, but dip stick +, ++, and +++ usually approximates with the three albuminuria stages.

79 GFR and albuminuria/proteinuria are used to classify CKD because GFR is a well-established marker

80 of renal excretory function and albuminuria is an indicator of renal barrier dysfunction, i.e.

81 glomerular injury. Both have found to be reliable predictors of long term CKD outcomes

82 As the kidney is formed by many independent functional and anatomical 'units', the nephrons GFR,

83 can be expressed by the equation:  $GFR_{(Total)} = GFR_{(single\ nephron)} \times \text{number of nephrons}$ . This implies that

84 when the number of nephrons declines, total GFR will not change as long as single nephrons can

85 increase their individual GFR (known as single-nephron GFR (SNGFR). Vice versa, a decline in total

86 GFR implies a significant loss of nephrons with remnant nephrons probably operating at their

87 maximum possible SNGFR. That is, CKD can be thought of generally as a loss of functional nephrons

88 but usually represents loss in nephron number. Furthermore, the KDIGO stages are derived from

89 large databases of general, high risk and nephrology populations. The categories define risk of

90 progression to ESKD that is defined as G5 ( $GFR < 15 \text{ mL/min/1.73 m}^2$ ) and a number of other

91 outcomes including risk of cardiovascular disease (CVD), death, AKI, infections, and hospitalizations.

92 The KDIGO staging has proven to be very instrumental in decision making on patient

93 management.

94 Whether CKD should be diagnosed and staged using absolute thresholds irrespective

95 of age remains controversial<sup>2, 3</sup>. The mGFR in healthy adults aged 20-40 years is about 107

96 ml/min/1.73 m<sup>2</sup> and declines at a rate of about 0.7 ml/min/1.73 m<sup>2</sup> per year<sup>4, 5</sup>. By age 75

97 years, many otherwise healthy individuals (without significant co-morbidity) will have lost

50% of their nephrons and their GFR that was present at age 25 years <sup>6</sup>. A substantial number of older healthy individuals have eGFR <60 ml/min/1.73 m<sup>2</sup> and no abnormal albuminuria (KDIGO CKD G3a A1) meeting the KDIGO criteria for CKD albeit having only a small increase in relative risk of all-cause mortality <sup>7, 8</sup>. The threshold of GFR that should be used to detect CKD in younger persons is equally controversial <sup>9</sup>. The upper and lower limits for mGFR in a 25 year old healthy person being considered as a living kidney donor is about 136 to 78 ml/min/1.73 m<sup>2</sup> respectively <sup>5</sup>; some have suggested that a threshold of <75 ml/min/1.73 m<sup>2</sup> would be more appropriate for young adults, and values below this threshold are associated with a significantly increased relative risk of all-cause mortality and ESKD <sup>10</sup>.

The etiology of the impaired kidney function is important, and thus in addition to classifying the severity of CKD by GFR and albumin levels, understanding the risk factors or causes of CKD is essential (Box 1), and recommended by the guidelines <sup>1</sup>. In this Primer, we discuss the global prevalence of CKD, the different diseases underlying poor nephron endowment or nephron loss, the pathophysiology of CKD progression, the diagnosis, screening, and prevention of CKD, and CKD management to improve outcomes and quality of life. Finally, we name several research domains potentially offering improvements for CKD management in the near future.

## **[H1] Epidemiology**

Rates of age-standardized death and disability due to most non-communicable diseases have decreased over the past 20 years, but such favourable trends are not present for CKD. The Global Burden of Disease study reports indicate an increase burden of CKD (with substantial worldwide variation) to which diabetes mellitus seems to be the most important contributor <sup>11-13</sup>. CKD as a cause of mortality has increased over the last 25 years from 21<sup>st</sup> to 13<sup>th</sup>, and now contributes 1.35% of the global burden of disability life years lost, growing at a rate of 1% per annum <sup>11, 13, 14</sup>. Note that most prevalence data are based on levels of GFR only, without consideration of albuminuria, based on the first CKD classification system reported in 2002.

## [H2] Prevalence

CKD stage G3–5 prevalence in adults varies worldwide, with values reported as 1.7% in China<sup>15</sup>, 3.1% in Canada<sup>16</sup>, 5.8% in Australia<sup>17</sup> and 6.7% in the USA<sup>18</sup>. In Europe the range is slightly narrower: from 2.3% in Germany<sup>19</sup>, 2.4% in Finland<sup>20</sup>, 4.0% in Spain<sup>20</sup> to 5.2% in England<sup>21</sup>. Such numbers should be viewed with caution because they are often based on a single eGFR assessment (that is not considering the actual definition, which includes the factor of time (present for >3 mo; thus it is possible that positive “CKD cases” may overestimate the true prevalence of CKD<sup>22</sup>. The epidemiology of CKD in low and middle-income countries (LMICs) is poorly characterized due to the lack of community-based studies, inconsistent assessment of kidney function and non-standardized or non-calibrated approaches<sup>23</sup>. Nevertheless, in South-East Asia, some Latin American countries (such as Mexico) and in sub-Saharan Africa, when assessed, the prevalence of CKD appears to be consistent with the estimates of 10-16%<sup>23-25</sup>.

## [H2] Risk factors

CKD is more common in people over 65 but the probability of progression to ESKD is higher in younger people with CKD, albeit sometimes over long period of times<sup>26</sup>. Interestingly, while the prevalence of CKD is higher in women than in men, men are more likely to progress to ESKD<sup>26</sup>. The most common underlying diseases are diabetes mellitus and hypertension, particularly in high and middle income countries. In those with diabetes, CKD prevalence is estimated in 30- 40%. Whether this is due to diabetes per se or due to microvascular disease is not known. However, in LMICs, CKD is often due to infectious diseases and glomerulonephritis (a group of diseases that lead to inflammation of the glomerulus)<sup>27</sup>. Current and future changes in socio-economic circumstances and population age distributions will increase the absolute number of people with CKD in these countries, where numbers of elderly persons are rising, and with increasing diabetes and obesity epidemic, may change the cause of CKD in those populations as well. Furthermore, low birth weight is associated

with CKD later in life; the global risks of preterm birth and low birth weight are around 10% and 15%, respectively. Thus, millions of children are born at risk of CKD later in life and are found at the lower percentile of age-matched GFR<sup>28, 29</sup>. Specific populations are at higher risk for CKD, in part due to genetic factors, and others due to interaction of genetic and environmental factors. Those groups at higher risk include, in alphabetical order: Aboriginal Australians, African Americans, Hispanics, indigenous populations in Canada, South Asians, Oriental Asians, and Pacific Islanders.

Endemic forms of CKD suggest regional triggers, which are often difficult to define among potential candidates such as specific infections, toxins, behaviours or climate-related factors<sup>30</sup>. Reports of chronic interstitial nephritis or CKD of undetermined origin (CKDu) in sugar cane and other agricultural workers in Latin America, Sri Lanka, India, and more recently in Cameroon, Mexico, and Australia, are examples of this<sup>30-32</sup>.

161161

## **[H2] Children**

Little is known about CKD in children because of the absence of registries, and that they are not included in many clinical studies. In Europe, the 2014 incidence of paediatric ESKD was 5.7 per million age-related population (pmarp) in children aged 0-14 years and the prevalence 32.2 pmarp<sup>33</sup>. Earlier estimates suggested the incidence and prevalence were 8.3 pmarp and 58 pmarp, respectively, in children aged 0-19 years<sup>34</sup>, which is lower than 14.7 pmarp and 103.9 pmarp for the age group 0-21 years in the United States<sup>35</sup>. In high income countries, congenital disorders are responsible for the majority of cases of paediatric CKD; by contrast, in acquired causes, such as infection and glomerular diseases, predominate in LMICs<sup>36</sup>.

171171

## **[H2] Kidney replacement**

Understanding the information on kidney replacement therapy in the context of CKD is important for identifying gaps and focusing on solutions to those gaps<sup>37</sup>. Often countries do not know the number of patients with prevalent CKD but do have information on dialysis numbers. Given that not all



people progress to ESKD, estimates of those with CKD can be extrapolated; conversely if CKD rates are known then numbers on dialysis can reveal inequities in availability of dialysis. Data on the incidence of kidney replacement therapy for ESKD can only be obtained from countries with dialysis registries. Data are missing in particular from LMICs, where such registries do not exist. In 2014, incidence of kidney replacement therapy varied from 49 per million population (pmp) in Bangladesh to as high as 455 pmp in Taiwan <sup>38</sup>. The majority of patients started kidney replacement therapy on dialysis, because pre-emptive transplantation as an initial modality is not freely available. Kidney transplant rates differed substantially by country from 1 pmp in Bangladesh to 60 pmp in Jalisco (Mexico). There was also huge variation in the prevalence of kidney replacement therapy (FIG. 2): from 113 pmp in Bangladesh to 3,219 pmp in Taiwan <sup>38</sup>.

In many European countries, more than half of all kidney replacement therapy patients are transplant recipients <sup>38</sup>. This is in contrast to the situation in some Asian countries like Taiwan, Japan and the Philippines where kidney transplantation is hardly performed <sup>38</sup>. There are multiple reasons why transplantation is not available despite the availability of expensive dialysis services: cultural, socioeconomic and health care infrastructure deficiencies (lack of biopsy services, lack of surgeons, lack of immunology laboratories) account for many of these. Existence of available dialysis and transplant services has not been systematically documented; however the Global Kidney Health Atlas [<sup>38</sup>; full report at [www.theisn.org](http://www.theisn.org)] describes availability of kidney replacement therapy worldwide. Note that the registry data for dialysis and transplantation described above does not reflect the true need for kidney replacement therapy, which may account for the wide variability in incidence and prevalence. Estimates of unmet need vary from 2 to 7 million people per year <sup>39</sup>. Note that availability and accessibility are not the same, and even when services are available in a country or region, not all individuals may have access to them (depending on cost reimbursement, demand, and specific policies).

## [H1]Mechanisms/pathophysiology

### [H2] Nephron loss and compensation

In humans, nephrons are generated from the 12<sup>th</sup>-36<sup>th</sup> week of gestation with a mean number of 950,000 per kidney in a range from approximately 200,000 to >2.5 million<sup>40</sup>. No new nephrons can form upon injury and, during growth from childhood to adulthood, the available nephrons increase in size to accommodate increased renal demands. However, as people age, GFR declines (FIG. 3). Although nephrons can deal with transient increases in filtration load (such as upon food and fluid intake) by transient increases in SNGFR (“renal reserve”)<sup>41, 42</sup>, longer or persistent increases in body mass (for example, during pregnancy or obesity) promote nephron hypertrophy as the compensatory mechanism. Any injury- (or kidney donation-)related nephron loss may have the same effect (FIG. 4). Indeed, either severe kidney injury or combinations of injury with ageing-related nephron losses — especially in individuals with poor nephron endowment and/or obesity — accelerates persistent increased SNGFR and loss of remnant nephrons<sup>43</sup>.

Remnant nephron hypertrophy is triggered by persistent elevations of SNGFR and filtration pressure (that is, glomerular hypertension) across the glomerular filtration barrier, which implies glomerular hyperfiltration. Specifically, glomerular hyperfiltration and hypertension together promote the release of tumour growth factor- $\alpha$ /epithelial growth factor receptor<sup>44, 45</sup>, leading to nephron hypertrophy that reduces glomerular hypertension by increasing filtration surface<sup>46</sup>. Indeed, increased SNGFR and remnant nephron hypertrophy allows kidney donors to maintain an apparently “normal” renal function, despite lacking 50% of nephrons. Obviously, kidney donation does not necessarily cause CKD progression when donors are carefully selected for good nephron endowment, the absence of obesity, diabetes, and ongoing nephron injury<sup>47, 48</sup>. However, in other circumstances, hyperfiltration-driven increases in glomerular dimensions can potentially be harmful<sup>42, 46, 49-51</sup>. Beyond a certain threshold of hypertrophy, increasing podocyte (which are key octopus-shaped cells that maintain the glomerular filtration barrier of the nephron shear stress promotes

228 podocyte detachment, focal segmental glomerulosclerosis (FSGS, a pathological entity in which renal  
229 injury results in sclerotic lesions in segments of glomeruli), global glomerulosclerosis and subsequent  
230 nephron atrophy, a vicious cycle further reducing nephron number and the SNGFR of remnant  
231 nephrons (FIG. 5)<sup>44, 46, 52-55</sup>.

232

## 233 [H2] Impaired glomerular filtration and fibrosis

234 Persistent podocyte hypertrophy and glomerular hyperfiltration, maintained by angiotensin II  
235 production, ultimately aggravate podocyte loss and proteinuria, eventually impacting on glomerular  
236 filtration. Angiotensin-II, a peptide hormone that is part of the renin-angiotensin system (RAS) and  
237 drives vasoconstriction and aldosterone secretion (and thus sodium retention and an increase of  
238 blood pressure) directly impairs the glomerular barrier sieving function, possibly via inhibiting  
239 expression of the podocyte protein nephrin, a structural component of the slit diaphragm necessary  
240 for maintaining the glomerular filtration barrier independently of its hemodynamic effects<sup>56</sup>.  
241 Angiotensin-II possibly also contributes to the dysregulated response of parietal epithelial cell  
242 precursors along Bowman's capsule, generating FSGS lesions instead of replacing lost podocytes<sup>57</sup>.  
243 This structural remodelling of the glomerular tuft barrier presents clinically as proteinuria.  
244 Proteinuria not only serves as a marker for nephron damage but also predicts CKD progression<sup>44, 58</sup>,  
245<sup>59</sup>. Mechanistically, albuminuria also impairs the capacity of parietal epithelial cells to regenerate  
246 podocytes<sup>44</sup>, instead further promoting the formation of FSGS lesions (FIG. 5)<sup>60, 61</sup>.

247

248 CKD progression also involves non-specific wound healing responses including interstitial fibrosis.  
249 Albuminuria and complement, and infiltrating immune cells activate proximal tubular epithelial cells  
250 to induce the secretion of and pro-fibrotic mediators followed by interstitial inflammation and  
251 fibrosis<sup>62</sup>. Interstitial fibrosis is frequently considered as an additional factor driving further nephron  
252 injury, e.g. via promoting renal ischemia<sup>62</sup> but, as in other organs, scar formation may also be  
253 essential to mechanically stabilize the remaining nephrons<sup>63</sup>. The increased tubular transport

workload of remnant nephrons also involves anaerobic metabolism, intracellular acidosis, and endoplasmic reticulum stress — all promoting secondary tubular cell injury<sup>44, 60</sup>.

256256

## **[H2]Risk factors**

Several factors can contribute to the pathogenesis of CKD, including low birth weight, pregnancy, obesity, diabetes, and ageing. Each of these scenarios contributes different factors that lead to and/or exacerbate nephron loss, promoting the cycles of injury and ultimately resulting in kidney failure.

262262

### **[H3]Prematurity and low birth weight.**

Newborns with low birth weight (owing to preterm birth or intrauterine growth restriction) frequently display incomplete kidney development<sup>64-66</sup>. Depending on the severity of prematurity, poor nephron endowment can cause either early childhood CKD or CKD later in life<sup>64-70</sup>. The associated risk was estimated among US adolescents for every 13 individuals born at low birth weight, one had reduced GFR and one had raised systolic blood pressure, and this risk increases with age<sup>29</sup>. The risk of low birth weight infants (<2599 g) to experience CKD up to the age of 17 is fourfold increased compared to infants with a birth weight of >2500 g (FIG.3B)<sup>69</sup>. CKD onset at puberty is common in these individuals when rapid body growth exceeds the capacity of nephron number to accommodate the increasing filtration load<sup>71</sup>. In milder cases, poor nephron endowment at birth promotes the development of hypertension, CKD later in adults or a faster progression of glomerulonephritis to ESKD (FIG.3C)<sup>29, 66, 70, 72, 73</sup>. All of these factors increase the risk of cardiovascular disease.

276

### **[H3]Genetic factors.**

Congenital abnormalities of the kidney and the urinary tract (CAKUT) are the most common congenital abnormalities<sup>74</sup>. CAKUT present a wide spectrum of causes for kidney hypodysplasia,

280 imparting low nephron number and risk of CKD later in life<sup>75, 76</sup>. Genetic testing has revealed that  
281 ~20% of early-onset CKD (defined as CKD manifesting before 25 years of age) cases can be attributed  
282 to a monogenic cause<sup>77</sup>. Beyond CAKUT, these conditions include ciliopathies, cystic kidney diseases,  
283 tubulopathies, and podocytopathies causing FSGS<sup>75-78</sup>.

284       Until recently, monogenic causes of CKD were mostly reported in children or adolescents, but  
285 genetic variants also contribute as co-factors to CKD progression in adults (FIG. 4). For example, an  
286 *UMOD* gene variant, present on 17% of the alleles in the general population, is associated with CKD  
287 <sup>79-81</sup>. Another example is gene variants of apolipoprotein L1 (*APOL1*) in African Americans, which  
288 confer resistance to *Trypanosoma brucei* infections in sub-Saharan Africa<sup>82</sup>. However, these variants  
289 affect endosomal trafficking and autophagic flux, which ultimately leads to podocyte loss,  
290 glomerulosclerosis, nephron loss, and CKD progression<sup>83, 84</sup>. This may explain faster CKD progression  
291 in many patients with sub-Saharan ancestry<sup>82</sup>.

292292

**293 [H3]Obesity.**

294 A larger glomerular size on mildly obese (BMI>30 and <35) but otherwise healthy individuals suggests  
295 an increased SNGFR<sup>85</sup>. In general, the association between obesity and poorer renal outcomes  
296 persists even after adjustments for higher blood pressure and diabetes mellitus, suggesting that  
297 obesity-driven glomerular hyperfiltration directly contributes to nephron loss<sup>86, 87</sup>. Severe obesity  
298 alone or moderate obesity in combination with other factors such as genetic, low nephron number  
299 or aging can lead to development of proteinuria, secondary FSGS, and progressive CKD (FIG. 4)<sup>86, 88-91</sup>.

300300

**301 [H3]Pregnancy.**

302 The latter trimester of pregnancy involves volume expansion (that is, an increase in blood volume)  
303 causing an increase of total GFR by 50%<sup>92</sup>, implying a respective increase of SNGFR. These  
304 physiological adaptations are transient and without consequences in women with normal nephron  
305 number. However, in women with low nephron endowment or previous injury-related CKD (such as

306 in women with lupus nephritis), pregnancy-related glomerular hyperfiltration exacerbates remnant  
307 nephron glomerular hyperfiltration and hypertrophy. In some patients, final trimester pregnancy-  
308 related glomerular hyperfiltration then passes the threshold of compensation and triggers rapid CKD  
309 progression presenting with proteinuria and hypertension — a condition known as eclampsia. Pre-  
310 existing CKD G3A2 or higher, obesity, excessive body weight increase during pregnancy are well-  
311 known risk-factors for eclampsia <sup>93</sup>.

312312

### 313 [H3]Diabetes.

314 Diabetes is a well-known condition associated with massive glomerular hyperfiltration, evident from  
315 increased total GFR and renomegaly <sup>51</sup>. Hyperglycemia promotes the sodium-glucose transporter  
316 (SGLT)-2-driven reabsorption of sodium in the proximal tubule, a process that subsequently  
317 inactivates tubuloglomerular feedback and activates the RAS at the *macula densa* <sup>94, 95</sup>. The result is  
318 induction of a permanent dilation of the afferent arteriole and vasoconstriction of the efferent  
319 arteriole — permanently increasing SNGFR and total GFR <sup>96</sup>.

320 Although diabetes-driven glomerular hyperfiltration can be compensated for many years in  
321 younger patients with normal nephron number, it serves as a drastic accelerator single nephron  
322 hyperfiltration such as patients with low nephron endowment, injury- or ageing-related nephron  
323 loss, obesity or those who are pregnant <sup>97</sup>. Unfortunately, this is a highly prevalent combination of  
324 risk factors in older patients with type 2 diabetes, for which dual SGLT2/RAS inhibition can elicit  
325 potent nephroprotective effects <sup>98</sup>.

326326

### 327 [H3]Acute kidney injury.

328 Acute kidney injury (AKI) is a clinical syndrome defined by an acute deterioration of renal function  
329 resulting in the accumulation of metabolic waste and toxins, subsequent uremic complications, and  
330 potentially failure of other organs <sup>99</sup>. AKI is highly prevalent in hospitalized patients and can imply  
331 irreversible losses in nephron number<sup>100</sup>. In Western countries AKI occurs in both outpatient and

inpatient settings, the latter of which is simpler to document, and has been the focus of multiple papers describing the phenomenon and aiding in the understanding of the strong association between AKI and CKD. The causes of non hospital/institution-based AKI are diarrhea, infections, dehydration, medications, while in hospital it can be attributed to these same factors and exposures to nephrotoxins (dye) and is mostly observed in patients with multiple morbidities<sup>101</sup>. By contrast, in LMICs and tropical countries, AKI occurs frequently outside the hospital setting following episodes of diarrhoea, infections and obstetric complications<sup>102</sup>. Nephrotoxins can also cause AKI-related nephron loss inside and outside hospitals; for example, neonates treated with aminoglycosides, cancer patients receiving chemotherapy or communities exposed to environmental toxins such as heavy metals or aristolochic acid can experience AKI episodes<sup>30</sup>.

342342

### **[H3]Ageing.**

The slope of GFR decline varies among individuals depending upon age (FIG. 3), genetic factors, blood pressure, diseases implying kidney injury and body weight. Histologically, kidney ageing presents as global glomerulosclerosis, the respective atrophy of entire nephrons, and subsequent interstitial fibrosis<sup>53, 85</sup>. Whether ageing-related nephron loss is associated with hypertrophy (and glomerular hyperfiltration) of remnant nephrons is not consistently reported in the literature<sup>53, 85</sup>, but the analytical difficulties on how to precisely assess nephron number, glomerular volume, and how to acknowledge the different functions of juxtamedullary versus cortical nephrons can affect the interpretation of such data<sup>53, 85</sup>. Ageing is associated with decreasing podocyte density and total numbers<sup>53</sup>. Endomitosis-related mitotic catastrophe and podocyte detachment may contribute to glomerulosclerosis<sup>53, 103,104</sup>.

354354

### **[H2]Systemic effects**

The kidney is involved in multiple complex hormonal processes important in anemia, bone integrity, in regulation of acid base and electrolyte homeostasis, as well as blood pressure control

358 through neuroendocrine and volume sensors. As nephron mass declines, patients will suffer from  
359 complications associated with dysregulation of many of these systems. Anemia, vitamin D deficiency,  
360 hyperparathyroidism, acidosis, hyperkalemia and hyperphosphatemia, hyperuricemia, as well as  
361 hypertension and expansion of effective circulating fluid volume are all clinical manifestations of  
362 these derangements. Interestingly, they do not occur in all individuals at the same point in the  
363 progressive loss of kidney function, and there are some maintain excellent tubular/ excretory  
364 function despite derangements in hormonal function (i.e. severe anemia, and normal electrolytes).  
365 Not all of the derangements are symptomatic, and the severity of the symptoms is variable  
366 between individuals. They include: disorders of fluid and electrolytes, mineral and bone disorder,  
367 anemia, hypertension, dyslipidemia, endocrine abnormalities, in children growth impairment,  
368 decreased clearance of renally excreted substances from the body (eg, hyperuricemia), metabolic  
369 acidosis. Related symptoms may be fatigue, anorexia, weight loss, pruritis, nausea, vomiting,  
370 muscle cramping, edema, shortness of breath, to name a few. None are specific for CKD.

371371

### 372 [H3] Fluid and electrolyte abnormalities.

373 **Sodium and water balance** — Sodium and intravascular volume balance are usually maintained via  
374 homeostatic mechanisms until the GFR falls below 10 to 15 mL/min per 1.73 m<sup>2</sup>. However, the  
375 patient with mild to moderate CKD, despite being in relative volume balance, is less able to respond  
376 to rapid infusions of sodium and is, therefore, prone to fluid overload. In some cases, especially with  
377 an acute water load, hyponatremia and hypertension may occur as a consequence of fluid retention.  
378 Some patients, such as those with nephronophthisis and some with obstructive uropathy, have an  
379 impaired ability to concentrate urine, and have symptoms of polyuria. These children are at risk for  
380 hypovolemia, as they will continue to have large urine losses even when they are volume depleted.  
381 **Hyperkalemia** — In children with CKD, hyperkalemia develops due to reduced GFR causing  
382 inadequate potassium excretion. Also, potassium excretion is dependent upon an exchange with  
383 sodium at the distal tubule. A low GFR decreases delivery of sodium to this site where there is



reduction in the exchange rate with potassium into the urinary lumen. Other contributory factors for hyperkalemia include: high dietary potassium intake, catabolic conditions with increased tissue breakdown, metabolic acidosis, secondary type IV renal tubular acidosis (RTA) in some patients with obstructive uropathy, decreased renin production by the juxtaglomerular apparatus, primary or secondary hypoaldosteronism related to RAS inhibitor-related impaired cellular uptake of potassium

### **[H3]Metabolic acidosis.**

Metabolic acidosis is observed in patients with advanced CKD and is related to the fall in total ammonium excretion that occurs when the GFR decreases to below 40 to 50 mL/min per 1.73 m<sup>2</sup> (GFR category G3). In addition, there is a reduction in both titratable acid excretion (primarily as phosphate) and bicarbonate reabsorption. As the patient approaches ESKD, the serum bicarbonate concentration tends to stabilize between 12 and 20 mEq/L. A level <10 mEq/L is unusual, as buffering of the retained hydrogen ions by various body buffers prevents a progressive fall in the bicarbonate concentration. In children with CKD, metabolic acidosis has a negative impact on growth.

### **[H3] Anemia.**

The anemia of CKD is due primarily to reduced renal erythropoietin production. The anemia of CKD is principally normocytic and normochromic. By comparison, the finding of microcytosis may reflect iron deficiency or aluminum excess, while macrocytosis may be associated with vitamin B12 or folate deficiency. If left untreated, the anemia of CKD is associated with fatigue, weakness, decreased attentiveness, increased somnolence, and poor exercise tolerance.

### **[H3]Mineral bone disease.**

Chronic kidney disease-mineral and bone disorder (CKD-MBD) presents as a broad clinical spectrum encompassing abnormalities in mineral metabolism, bone structure, and extraskeletal calcifications

409 that are found with progressive CKD. Patients with mild CKD (G2 KDIGO) may have reduced serum

410 calcidiol and/or calcitriol levels, and an elevated serum parathyroid hormone (PTH) and fibroblast  
411 growth factor 23 (FGF-23) level <sup>105</sup>. Patients with more advanced CKD-MBD have bone pain, difficulty  
412 in walking, and/or skeletal deformities and a higher risk of fracture <sup>106</sup>.

413413

#### 414 [H3]Hypertension.

415 Hypertension can be present in the earliest stages of CKD, and its prevalence increases with  
416 progressive declines in GFR. Hypertension is high in children with CKD, ranging from 54 to 70 percent  
417 of patients <sup>107</sup>. Hypertension is due to activation of the RAS and volume expansion. In some cases,  
418 hypertension arises from corticosteroids or calcineurin inhibitors such as [cyclosporine](#) or [tacrolimus](#)  
419419 used to treat the underlying kidney disease.

420420

#### 421 [H3]Dyslipidemia.

422 Abnormal lipid metabolism is common in patients with CKD and is one of the primary factors that  
423423 increase the risk for CVD.

424424

#### 425 [H3]Hyperuricemia.

426 Elevated uric acid levels may develop in patients with CKD due to decreased urinary excretion. Serum  
427 uric acid greater than 7.5 mg/dL is an independent risk factor for accelerated progression of CKD and  
428428 should be treated to have a better outcome.

429429

#### 430 [H3]Cardiovascular disease.

431 CVD is the leading cause of death in patients with CKD worldwide <sup>14</sup>. The increased incidence of CVD  
432 is due to the high prevalence of CVD risk factors, such as hypertension, dyslipidemia, hyperuricemia,  
433 abnormal glucose metabolism obesity. Young adults (25 to 34 years) with CKD have at least a 100-  
434 fold higher risk for CVD-related mortality compared with the general population <sup>108</sup>. Patients with a

435 glomerular etiology of CKD and proteinuria were more likely to have CVD risk factors. The CKD-

related cardiovascular alterations resemble all aspects of an accelerated ageing process associated with a shortening of relative telomere length <sup>109</sup>. The vasculature can be affected by both, atherosclerosis and arteriosclerosis, with lipid-rich plaques but also abundant media calcification. The burden of atherosclerotic CVD increases in the early stages of CKD, and the burden of non-atherosclerotic CVD increases in the more advanced stages of CKD. The „two“ diseases involve different factors that cause distinct changes in the risk factor profile and contribute differently to outcomes during the course of CKD. Adaptive changes of the heart include left ventricular hypertrophy (LVH) but also dilatation with subsequent both, systolic and diastolic dysfunction. There are two different patterns of LVH: concentric LVH, which occurs in the presence of hypertension, and eccentric LVH, which is associated with volume overload and anemia. Early and sustained induction of fibroblast growth factor-23 was recently discovered as a driver of LVH in CKD <sup>110</sup>.

The absolute risk of cardiovascular events in individuals with pre-dialysis CKD is similar to that of patients with established coronary artery disease in the general population <sup>111</sup>, and the increase in risk multifactorial: a higher prevalence of insulin resistance <sup>112</sup>, high blood pressure, vascular calcification <sup>113, 114</sup>, inflammation and protein-energy wasting <sup>115</sup>. ESKD is associated with a range of metabolic abnormalities, the so-called milieu of uremic toxicity <sup>116</sup>, activation of the neuro-hormonal axis <sup>117</sup>, vitamin D receptors <sup>113</sup>, that may all contribute to accelerated ageing of the vasculature and damage to the heart. Hemodialysis itself may have a direct negative effect on the heart, so-called myocardial stunning <sup>118</sup>. As a consequence the cardiac and vascular mortality are several times higher in patients with low GFR or on dialysis than in the general population. Thus, the risk of CVD in patients who require dialysis depends largely on their cardiovascular health at dialysis initiation. In patients with healthy arteries, the pre-dialysis management strategy should be continued to prevent new cardiovascular lesions. Consequently, risk factors for CVD should be managed intensively in the pre-dialysis period, during transition, and at dialysis initiation.

### **[H3]Endocrine dysfunction.**

462 In patients with CKD, the following endocrine systems become dysfunctional as kidney function  
463 progressively deteriorates. Each of these is discussed in greater detail separately. There are  
464 abnormalities in gonadal hormones in both male and female patients, which can results in reduced  
465 fertility and sexual problems. In children, these abnormalities result in delayed puberty in two-thirds  
466 of adolescents with ESKD <sup>119</sup>. End-organ resistance to GH due to increased levels of insulin growth  
467 factor binding proteins appears to play a major role in growth impairment in children with CKD <sup>120</sup>.  
468 Abnormalities in thyroid function can also be observed.

### 469 [H3]Neurological signs.

470 Uremia is associated with cognitive alterations in adults and lower performance in all neurocognitive  
471 domains development in children. The neurologic findings can range from seizures and severe  
472 intellectual disability to subtle deficits.

### 473 [H3]Sleep and fatigue.

474 Daytime sleepiness and fatigue are common and increase with decreasing kidney function. Sleep  
475 disorders (restless leg syndrome/paroxysmal leg movements, sleep-disordered breathing, excessive  
476 daytime sleepiness, and insomnia) are also common

### 477 [H3]Uremia.

478 The onset of ESKD (ie, GFR category G5) results in a constellation of signs and symptoms  
479 referred to as uremia. Manifestations of the uremic state include anorexia, nausea, vomiting, growth  
480 retardation, peripheral neuropathy, and central nervous system abnormalities ranging from loss of  
481 concentration and lethargy to seizures, coma, and death. Patients who are uremic also have an  
482 increased tendency to bleed secondary to abnormal platelet adhesion and aggregation properties.  
483 Pericardial disease (pericarditis and pericardial effusion) is an indication to institute dialysis. The  
484484 initiation of RRT should be considered  
485485

486486

## **487 [H1] Diagnosis, screening and prevention**

488 The clinical presentation of CKD depends upon the underlying disorder and the severity of renal  
489 impairment. Patients with early stages of CKD G1-2 are usually asymptomatic. From CKD G3-5  
490 patients may experience weakness related to anemia and polyuria. Only in late stages and in  
491 untreated patients symptoms may include anorexia, vomiting, weakness, and fatigue, which are  
492492 referred to as symptoms of uremia.

493493

## **494 [H2]Detection and diagnosis**

495 CKD can be detected during a periodic health assessment in an asymptomatic person or during  
496 evaluation of individuals at risk for CKD (Box 1); as a consequence of the incidental finding of  
497 abnormal laboratory values in connection with an acute or chronic illness; during an investigation of  
498 symptoms and/or signs relating to the kidneys or urinary tract (such as haematuria); or during  
499 discovery of abnormal laboratory values in a population-based screening program. Importantly, the  
500 two biochemical parameters (GFR and proteinuria) used in the aforementioned KDIGO matrix<sup>1</sup> define  
501 and classify a “generic” form of CKD, and adding an etiological diagnosis is both highly desirable and  
502 recommended by KDIGO (The Cause/GFR/Albuminuria [CGA] classifications system), whenever  
503 possible, such that the underlying conditions can be treated first to halt progression of CKD.  
504 Progression is defined according to changes in eGFR by KDIGO<sup>1</sup>. Several tests can be performed to  
505 confirm a CKD diagnosis and identify its cause. It must be stressed that a diagnosis of CKD, according  
506 to the KDIGO construct, requires persistence or progression of the defining abnormality for at least 3  
507507 months. A single value of GFR or albuminuria is insufficient and if used for diagnosis of CKD will lead

508508

## **509 [H3] Measuring and estimating GFR.**

510 First, the assessment begins with measurement of serum creatinine concentration (under steady-  
511 state conditions) and applying formulas for estimated GFR (eGFR – creatinine, like CKD-EPI eGFR-

creatinine). It must be recognized that the results of these creatinine based tests can be influenced by changes in muscle bulk (atrophy or hypertrophy), dietary intake of cooked red meat (strict vegan diet) and alterations in tubular secretion of creatinine from exposure to drugs (e.g. trimethoprim-sulfamethoxazole)<sup>121, 122</sup>. Alternative approaches using serum cystatin\_C concentrations have also been proposed. While not influenced by muscle bulk and diet, the cystatin C -based formulas for eGFR can be affected by inflammation, obesity, thyroid disease, diabetes, and steroid administration<sup>123</sup>. Second, some eGFR formulas have not been extensively validated in older subjects and may not apply to Asians or Africans<sup>124, 125</sup>. Third, the requirements for inclusion of demographic variables of age and gender, to correct for differences in creatinine generation, may also create unwanted complications in determining prognostic implications of a calculated GFR. Newer eGFR formulas such as FAS (full age spectrum) or CKD-EPI using serum creatinine, cystatin C or a combination of Cystatin C or a combination of both have improved accuracy to predict mGFR<sup>126, 127</sup>. Although cumbersome and expensive, mGFR assessments using urinary clearance methodology can sometimes be needed, but applying methods of plasma clearance of Iohexol or of radiolabelled Iothalamate could avoid some of these issues. In well-defined circumstances, such as stratifying long term risks of unilateral nephrectomy for potential living kidney donors, such studies can be useful<sup>128, 129</sup>. As mentioned in the introduction, caution should be exercised in using a fixed and arbitrary threshold of <60ml/min/1.73m<sup>2</sup> of GFR alone (in the absence of abnormal proteinuria or imaging) for the diagnosis of CKD in older or elderly adults. A GFR of 45-59ml/min/1.73m<sup>2</sup> is fairly common in otherwise healthy seniors, depending on their age, due to the normal physiologic loss of nephrons and GFR with organ senescence<sup>130</sup>.

533533

### **534 [H3]Measuring proteinuria.**

Abnormal rates of urinary excretion of albumin or total protein are essential for detection of CKD when GFR is normal and contribute to the assessment of prognosis<sup>131</sup>. Proteinuria (or albuminuria) can be determined in multiple ways, including simple “dip stick” qualitative methods,



point-of-care urinary albumin concentration tests, random un-timed urine samples for calculation of urine protein (or albumin) to creatinine ratios (UPCR or UACR in mg/mg or mg/mmol), or timed 24 hour urine collections and measuring absolute protein or albumin excretion<sup>132, 133</sup>. Each of these has advantages and pitfalls. But it is important to recognise that not all patients with CKD have abnormal urinary protein excretion. For example, early in the course of Autosomal Dominant Polycystic Kidney Disease the urinary protein excretion is normal only slightly increased<sup>134</sup>.

Urinary protein or albumin excretion is more variable than serum creatinine levels, and can be influenced by posture, activity, fever or drugs so multiple specimens must be collected to enhance reliability. UPCR and UACR methods can be influenced by the prevailing urinary creatinine excretion rate; i.e. low creatinine excretion (from sarcopenia) can increase UPCR or UACR values even at normal absolute protein or albumin excretion rates. Hence, adjusting for the effect of urinary creatinine excretion can enhance the accuracy of UPCR and UACR measurements<sup>132, 133</sup>.

In the KDIGO schema, UACR values are divided into three categories<sup>1</sup>, namely, normal or low, which is <30 mg/g creatinine (<3.0 mg/mmol, formerly “normo-albuminuria”); moderately increased, which is ≥30-299 mg/g creatinine (>3.0-29 mg/mmol, formerly “micro-albuminuria”); and severely increased, which is ≥300 mg/g creatinine (30 mg/mmol, formerly “macro-albuminuria”). Even with a normal eGFR, CKD can be diagnosed with persistent UACR of >30 mg/g creatinine. Each incremental increase in UACR is associated with an increased risk of mortality and ESKD, so sustained albuminuria (or proteinuria) is a powerful prognostic marker.

The corresponding “dipstick” (urinalysis test strip) values (and protein concentration in mg/dL) are negative (<10 mg/dL) to trace (10-15 mg/dL) for normal, 1+ (30 mg/dL) for moderate and 2+ (>100 mg/dL) or greater for severe proteinuria. Persistent proteinuria of >1+ is a good predictor of a tendency for CKD progression, i.e. GFR decline of > 5 ml/min/1.73 m<sup>2</sup>/year or 7 times the normal rate of loss with ageing<sup>135</sup>. Thus, albuminuria or proteinuria allow early detection of CKD (see Screening below), but several forms of progressive CKD can present with normal or only slightly increased albumin or protein excretion, especially tubulo-interstitial diseases such as autosomal

564 dominant polycystic kidney disease <sup>134</sup>. Marked proteinuria (in excess of 3.5 g/d in an adult),  
565 especially when accompanied by a reduction in serum albumin concentration (referred to as  
566 “nephrotic syndrome”) nearly always implies a diagnosis of a primary or secondary glomerulopathy  
567 underlying CKD <sup>136</sup>.

568568

### 569 [H3]Biopsy and pathology.

570 Percutaneous kidney biopsy is a very valuable tool in assessment of the underlying cause for CKD.  
571 The indications for performance of a renal biopsy in a patient with CKD depends upon the benefits to  
572 be obtained (precise diagnosis, better prognosis, appropriate therapy) and the risks of a biopsy-  
573 related complications. Kidney biopsies are commonly recommended for adult patients with  
574 nephrotic syndrome (urine protein excretion of >3.5 g/d and serum albumin levels <3.5 g/dL) but  
575 may also be indicated for evaluation of unexplained rapidly progressive loss of kidney function,  
576 persistent hematuria and low-grade proteinuria (0.5-3 g/d), or even isolated proteinuria (1-3 g/d) <sup>137</sup>.  
577 Depending on the circumstances leading to the procedure, the pathologic findings can vary widely,  
578 but in states of marked proteinuria glomerular diseases are most likely to be seen. The degree of  
579 tubule-interstitial scarring can provide useful prognostic information. The risks of renal biopsy are  
580 minimal in experienced hands, and complications are mostly related to post-biopsy bleeding. Fatal  
581 complications are rare (about 1:20,000). Major complications, such as nephrectomy or transfusion  
582 requiring bleeding are more common (about 1:250-500) <sup>138, 139</sup>.

583583

### 584 [H3]Other tests.

585 Continuing advances in the field of serum and urine proteomics, microRNA biology and in serology  
586 are providing many new powerful and non-invasive tools to identify specific diseases or groups of  
587 diseases that may revolutionize the approach to detecting and diagnosing CKD in the future <sup>140</sup>.  
588 These new tools may also expand the horizon of prognosis into new areas beyond GFR and  
589 proteinuria estimation — giving rise to exciting new possibilities for “precision” medicine whereby

care of CKD is personalized based diagnostic and prognostic characteristics. Unfortunately, many patients with CKD are only recognized in the later stage of the disease (Categories G3B-G5) where CKD complications such anemia, metabolic acidosis, mineral-bone disease provide additional diagnostic clues.

In addition, both detection and diagnosis of CKD, also rely on renal imaging (ultrasonography, CT and MRI), careful examination of the urinary sediment, and specialized biochemical and serologic tests suitable to detect specific disorders causing CKD (Box 2). Imaging tests are particularly valuable as they provide information on kidney size, contours, location, and density as well as anatomy of the urinary drainage system (pelvis, ureters and bladder). Specific lesions, such as cysts, dilation of ureters or pelvis, calcification, masses, scars can provide valuable clues to the cause of CKD or even generate a specific diagnosis (such as autosomal dominant polycystic kidney disease or obstructive uropathy)<sup>141</sup>. Then urine sediment examination is important for the detection and quantification of haematuria, leukocyturia and casts.

Genetic testing is also emerging as an important tool for diagnosing CKD, particularly in children or young adults. Autosomal dominant polycystic kidney disease, podocytopathies causing steroid-resistant nephrotic syndrome, Fabry's disease, Alport syndrome, are other well-known entities requiring a genetic diagnosis. Using next-generation sequencing displays an unexpected genetic heterogeneity and alterations in numerous different genes in a significant proportion of not only familial or syndromic patients but also in sporadic cases of CKD. These observations imply the need for updating the current management in terms of diagnostic algorithms and therapeutic choices<sup>77, 142</sup>.

## **[H2]Screening**

In the context of CKD, screening can take two forms: population screening, for example, using "dipstick" urinary testing of school children or soldiers; or "opportunistic screening", whereby

physician encounters for other medical reasons can be used to screen for CKD. Population-based screening can be further divided into general population screening or “targeted” screening of high-risk population groups (such as diabetic or family members related to subjects with diagnosed CKD). Unfortunately, the benefits and harms of both forms of screening for CKD have not been rigorously tested in long-term prospective studies, so the overall benefits and harms of population-based screening for CKD are poorly understood and further trials are needed <sup>143, 144</sup>. Population-based screening for CKD is not recommended by the United States Preventive Task Force largely due to insufficient evidence of benefit (or harm) <sup>145</sup>. Evidence in favor of case-finding (i.e., testing for CKD in people with recognized risk factors, such as hypertension or diabetes) is slightly better, but still incomplete. Accordingly, the American College of Physicians determined that current evidence was insufficient to evaluate the benefits (or harms) of screening and case-finding for CKD <sup>146</sup>. The position on screening for CKD varies widely around the world, with several countries having long-established programs (Japan and Singapore for example) and others that have introduced them as part of universal health care systems (The United Kingdom for example) <sup>147-151</sup>.

Both screening and case-finding for CKD are logistically hampered by the need for re-evaluation at a defined interval to fulfil the duration requirement for diagnosis. Therefore, one-off testing using eGFR or proteinuria has a high “false positive” detection/diagnosis rate, and possible misclassification of subjects by use of a fixed (non-age-sensitive) eGFR thresholds, as discussed. The potential harms of general population screening involve excessive follow-up diagnostic procedures, unnecessary referral of subjects erroneously diagnosed as having CKD, the anxiety induced by being labelled as having CKD, and potential impact on insurability. Nevertheless, several national kidney organizations advocate screening for CKD. Monte Carlo simulations support case-finding strategies in diabetic subjects for albuminuria or hypertension <sup>152</sup>, because early treatment may offer significant effects on delaying CKD progression and ESKD <sup>153</sup>. Some studies have suggested that testing for abnormal albuminuria may be an efficient way of stratifying populations for more intensive search for modifiable risk factors for CKD and cardio-vascular events, such as hypertension and diabetes <sup>154</sup>.

642 Indeed, abnormal proteinuria (even only slightly above the upper limit of normal) identifies people at  
643 greater risk for ESKD and/or cardiovascular morbidity and mortality <sup>155</sup>. As mentioned before,  
644 population screening for CKD using eGFR tends to substantially over-diagnose CKD in older subjects  
645 with no or minimal proteinuria. Opportunistic testing for CKD has much merit, especially if the  
646 subjects have other risk factors such as diabetes, hypertension, or a family history of CKD. In such  
647 patients an eGFR should be assessed along with an estimate of albuminuria or total protein excretion  
648 ("dipstick"), UACR or UPCR- adjusted for creatinine excretion rate). It also must be appreciated that  
649 older subjects with CKD G3 (as defined by KDIGO, see above) detected in screening programs or  
650 otherwise in primary care practices tend to have a rather benign prognosis, at least over the short  
651 term of 5 years or less. Shallow et al found a very low rate of ESKD (0.2%) and stable or remission  
652 of CKD was found in 53% of such subjects (average age 73 years at entry) after 5 years of follow-up  
653653 <sup>156</sup>.

654 Finally, there are a few special circumstances where testing of apparently healthy individuals  
655 for CKD may be indicated. For example, first degree relatives of a patient with autosomal-dominant  
656 polycystic kidney disease (ADPKD) are eligible for screening with renal ultrasound or MRI regardless  
657 of results of eGFR or proteinuria. Siblings of patients with Fabry's disease, Alport syndrome, or thin  
658 basement membrane nephropathy might also benefit from genetic analysis as well. African-  
659 Americans with hypertension or HIV infection may receive more informed prognosis by assessment  
660 of *APOL1* risk alleles, but population-based screening for *APOL1* risk alleles is not yet justifiable <sup>157</sup>

661661

## 662 [H2]Prevention

663 From a societal perspective, prevention of CKD is preferable to after- the-fact treatment of kidney  
664 disease at its end-stage by dialysis or transplantation. Both primary prevention (occurring before CKD  
665 is established) and secondary prevention (initiated to slow the rate of CKD progression or to affect  
666 the associated co-morbidities or complications; see below, Management) should be considered.

667 Primary prevention attacks the root causes of CKD and includes mitigating exposures to

nephrotoxic agents and events (Box 1). Reduction of the burden of infectious diseases (such as HIV, Malaria, *Streptococcus* infection) have already yielded some protection from CKD, but many challenges remain. Preventing obesity and the associated type 2 diabetes mellitus is a global challenge<sup>158</sup>. The discovery of a central role for sugar and fructose intake and metabolism in obesity can be cited as an example of progress with implications for primary prevention. Indeed, better glycemic control may also eventually prevent CKD and its progression<sup>153, 159-161</sup>. Improved recognition and reduction of the prevalence of AKI may also have dividends on prevention of CKD, especially in countries where AKI is common, under-recognized and under-treated such as equatorial Africa. Given the importance of low nephron endowment, fetal malnutrition and/or dysmaturity and manifested by low birth weight, global efforts to reduce fetal malnutrition and dysmaturity should have enormous “pay-back” in later years and focussed effects are beginning to address this important topic<sup>66</sup>.

680680

## 681 [H1] Management

Several aspects need to be considered when managing patients with CKD: controlling nephron injury, normalizing single nephron hyperfiltration, controlling CKD-related complications, and preparing the patient for kidney replacement therapy. At the core of these is the principle of ‘the earlier-the better’, which is the effort to reduce the progression to ESKD and optimize renal outcomes.

The impact of early therapy is well documented for Alport syndrome<sup>162</sup>. Initiating RAS blockade based on the genetic diagnosis before any signs of kidney disease can have dramatic effects on renal outcomes, whereas initiating RAS blockade as late as CKD G3 only somewhat delayed ESKD (FIG. 6)<sup>162</sup>. Further support comes from a posthoc analysis of clinical trials testing RAS blockade in diabetic kidney disease. The effect on gaining ESKD-free years was highest when RAS blockade was initiated at the time of microalbuminuria and lowest when initiated once a diagnosis of CKD G3 or G4 was made<sup>163</sup>. Therefore, early diagnosis and treatment are essential to prevent nephron loss from as early as possible.

694694

## 695 [H2]Controlling ongoing nephron injury

696 Nephron injury can be driven numerous triggers (Table 1), and abrogating these triggers will slow  
697 progression to CKD and ESKD. For example, genetic abnormalities can cause CKD either by fostering  
698 nephrocalcinosis <sup>164</sup>, cystic degeneration or by weakening epithelial integrity such as in genetic  
699 podocytopathies or in abnormal processing or storage of metabolites or glycoproteins <sup>78, 165</sup>. Specific  
700 cures for genetic kidney diseases exist in some forms and are mostly limited to enzyme replacement  
701 therapy or substrate supplementation (Table 1). The genetic basis of immune-mediated nephron  
702 injury is not yet fully explored but C3 glomerulonephritis or atypical hemolytic uremic syndrome  
703 (aHUS) can be controlled with complement inhibitors, an area of intense and promising research <sup>166</sup>.  
704 Most acute forms of immune-mediated nephron injury present either as vasculitis, immune complex  
705 glomerulonephritis or interstitial nephritis (including allograft rejection). These disorders can often  
706 be targeted with immunomodulatory drugs (and sometimes with plasma exchange) to limit nephron  
707 loss from attack by the humoral and/or cellular elements of the immune system <sup>167</sup>.

708 In contrast, in smoldering immune injury, such as in chronic IgA nephropathy, it is difficult to  
709 dissect CKD progression driven by immune versus non-immune mechanisms and the efficacy of  
710 immunosuppression versus RAS blockade and blood pressure control is less evident <sup>168</sup>. Kidney biopsy  
711 may establish the diagnosis and can also guide management by assessing the ongoing activity of  
712 immune injury versus irreversible damage, e.g. in lupus nephritis, IgA nephropathy or allograft  
713 dysfunction. Specific treatments are also available for CKD related to urinary tract obstruction,  
714 infections, and some forms of toxic injury (Table 1). However, even upon complete abrogation of the  
715 injurious trigger, recovery of lost nephrons is impossible.

716716

## 717 [H3]Preventing any avoidable injury of remnant nephrons.

718 Avoiding further episodes of AKI is crucial to minimize stress on the remnant nephrons in CKD  
719 kidneys. This implies patient education on avoidable nephrotoxins such as radio contrast media,

NSAIDs, certain antibiotics or other endemic or occupational toxins. Hypovolemic states as well as urinary outflow obstruction should be avoided. Additionally, not every asymptomatic leukocyturia implies bacterial infection and antibiotic treatment should be limited to the presence of dysuria, bacteriuria, and leukocyturia. Smoking cessation is essential minimize CVD <sup>169</sup>.

## **[H2] Normalizing single nephron hyperfiltration**

Rigorous RAS inhibition with ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) has the capacity to substantially reduce SNGFR and glomerular filtration pressure, which leads to a decline in not only proteinuria but also total GFR — and, hence, moderately increases serum creatinine levels <sup>170</sup>. At first, this serum creatinine increase is worrisome to patients (and physicians) and requires clarification that reducing hyperfiltration in remnant nephrons is the central strategy to retard CKD progression in patients with proteinuria. In contrast, ACEi or ARBs do not retard the progression of non-proteinuric forms of CKD such as ADPKD but still may have benefits on the associated cardiovascular complications <sup>171</sup>. ACEi or ARBs should be titrated to the maximal possible dose, while hyperkalemia can be corrected using loop diuretics or potassium-binding resins <sup>172</sup>. A moderate increase in serum creatinine levels indicates a decline in SNGFR, which is a powerful predictor of the intended nephroprotective effect <sup>173</sup>. Numerous RCTs have documented the class effect of RAS inhibitors to retard or even halt CKD progression <sup>44</sup>. Reducing dietary salt and drugs that support control of blood pressure and hyperlipidemia, often referred to as “remission clinic protocol”, may further reduce proteinuria and retard CKD progression <sup>174, 175</sup>. Such interventions are affordable and are of importance where kidney replacement therapy is not available or affordable.

Avoiding or correcting obesity can also reduce filtration load and glomerular hypertension; hence, a normal BMI is a treatment target to retard CKD progression <sup>176</sup>. Any immunosuppression-related benefit of using steroids in CKD may be counterbalanced by steroid-related obesity that drives glomerular hyperfiltration and secondary FSGS, which could explain why steroid treatment falls short in retarding progression of IgA nephropathy-related CKD <sup>168</sup>. Finally, concomitant diabetes



has important implications for CKD management <sup>177</sup>. Hyperglycemia maximizes glomerular hyperfiltration via SGLT2-driven vasodilation of the afferent arteriole of the remnant nephrons, which cannot be controlled by RAS inhibitors <sup>94</sup>. Recently, SGLT2 inhibitors have been shown to reverse this process and elicit profound additive nephroprotective effects on CKD progression <sup>98, 178</sup>. Their capacity to also reduce CVD (in patients with type 2 diabetes) <sup>178, 179</sup> provides a strong rationale for dual RAS/SGLT2 blockade in patients with diabetes and CKD.

## **[H2]Controlling CKD complications**

CKD is associated with a number of secondary complications that require management (Box 3), the most relevant of which in terms of overall mortality is CVD <sup>14</sup>. Cardiac and vascular alterations also arise from endocrine failure (e.g. lack of erythropoietin, vitamin D, parathyroid hormone), which causes anemia and secondary hyperparathyroidism <sup>180</sup>. Myocardial fibrosis is the final consequence of the multiple underlying causes.

Large randomized controlled trials in patients on hemodialysis have tested a number of different interventions intended to reduce cardiovascular events such as dialysis dose and flux, erythropoietin-stimulating agents, statins, RAS blockade, folic acid, cinacalcet or vitamin D derivatives but have largely been unsuccessful <sup>181-183</sup>. For example, statins may prevent cardiovascular events in patients on dialysis, but the magnitude of any relative reduction in risk is substantially smaller as compared to what can be achieved in CKD 2-4 <sup>183-186</sup>. For example, reduction of LDL cholesterol with simvastatin plus ezetimibe reduced the incidence of major atherosclerotic events more efficiently in patients with CKD G2-4 than with CKD G5 or 5D <sup>183</sup>. Hence, early intervention with standard-of-care is essential in patients with CKD 2-4. In parallel, similar concepts for cardiovascular protection are administered for progression of diabetic and non-diabetic kidney disease. For these patients, guideline-directed approaches to achieve target blood pressure through administration of RAS blockers, salt restriction and anemia prevention is the mainstay of therapy <sup>187</sup>,

771 <sup>188</sup>. Guidance is also available for the correction of acidosis and mineral and bone metabolism  
772 disorders (Box 3) <sup>189</sup>.

773773

## 774 [H2]Preparing for kidney replacement therapy

775 ESKD typically requires renal replacement therapy, although conservative treatment is a potential  
776 alternative option, especially in older adults with limited life span. Counseling on the options (kidney  
777 transplant, hemodialysis, peritoneal dialysis or no dialysis) should be coordinated by the nephrologist  
778 and involve a multidisciplinary team including the general practitioner. Early counseling is essential  
779 because informed patients are better prepared to face kidney failure. Indeed, late referral, i.e. at the  
780 time of ESKD, is associated with worse health status at the time of kidney replacement therapy  
781 initiation, higher mortality after starting dialysis, and decreased access to transplant <sup>190</sup>. However,  
782 one of the biggest challenges nephrologists face is to predict kidney disease progression, which does  
783 not follow a steady linear decline. This unpredictability often becomes a barrier to timely shared  
784 decision making between patients and physicians and could lead to adverse patient outcomes <sup>190</sup>,  
785 and may offset the relationship between the early pre-dialysis nephrology care for adults with late  
786 stage of CKD and improved outcomes <sup>191</sup>. KDIGO suggested that dialysis be initiated when one or  
787 more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-  
788 base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a  
789 progressive deterioration in nutritional status refractory to dietary intervention; or cognitive-  
790 impairment <sup>1</sup>. This often but not invariably occurs in the GFR range between 5 and 10  
791 ml/min/1.73m<sup>2</sup>. Moreover, living donor preemptive renal transplantation in adults should be  
792 considered when the GFR is <20 ml/min/1.73m<sup>2</sup>, and there is evidence of progressive and irreversible  
793 CKD over the preceding 6-12 months <sup>1</sup>.

794794

## 795 [H3]Hemodialysis.

796 In 1945 Willem Kolff was the first to successfully treat kidney failure of a patient by performing

hemodialys using an artificial kidney able to clear blood from uremic toxins<sup>192</sup>. Since then numerous technical innovations have optimized the procedure that meanwhile has become available (but not everywhere affordable) all over the world<sup>38</sup>. Preparing patients for hemodialysis involves referral for vascular access placement. The types of access include arteriovenous fistulae, arteriovenous grafts and central venous catheters (which are for short-term use) (FIG. 7A-C); arteriovenous access is the preferred option for hemodialysis, although there is no consensus about the optimal timing for creation, especially for arteriovenous fistulae<sup>193</sup>. To protect the blood vessels for permanent vascular access, attention should be taken to avoid venous puncture or intravenous catheter placement proximal to the wrist, which implies that venous puncture at the back of the hand still being possible. Arteriovenous access (either fistulae or grafts) is associated with better outcomes than central venous catheters<sup>194 195</sup>. Patients with a central venous catheter have poorer survival than those who subsequently convert to functional arteriovenous access<sup>196</sup>. Thus, a functional arteriovenous access is preferable for all patients in which the vascular status allows to install a fistula.

### **[H3]Peritoneal dialysis.**

Peritoneal dialysis is another way to eliminate uremic toxins from the blood using the peritoneal membrane as an exchange interface. For this a transcutaneous catheter is implanted into the peritoneal cavity that allows repetitive daily drainage and refills of dialysate fluid. After some hours of reaching equilibrium between uremic blood and fresh dialysate each dwell is expected to drain excess fluid, metabolic waste products including uremic toxins (FIG. 7D). There are published guidelines regarding insertion and perioperative management of peritoneal dialysis catheters. A peritoneal dialysis catheter may be ready for use after 2 to 3 weeks. However, there is marked variability in peritoneal dialysis catheter insertion techniques (open surgery, blind via trocar or blind via Seldinger technique) and perioperative management<sup>197</sup>. Interestingly, patients starting on peritoneal dialysis show better initial outcome and preservation of residual renal function, especially in the first 2 years as compared to patients on hemodialysis<sup>198</sup>.

823823

### **824 [H3]Kidney transplantation.**

825 When available, suitability for kidney transplantation should be evaluated according to age and co-  
826 morbidities, but it may take months to complete <sup>199</sup>. Co-morbidities such as cancer, chronic  
827 infections, cardiac or peripheral vascular disease, and the risk for medical noncomplicance are  
828 carefully evaluated in this process. Depending on the regional ratio of donors to recipients and on  
829 allocation rules, waiting time for a deceased donor kidney can vary from a few months (e.g. Belgium,  
830 Austria) to many years (e.g. Germany). Thus, the option of living kidney donation should be explored.

831 To test for eligibility, potential donors must undergo a comprehensive health assessment  
832 including tests for blood group and human leukocyte antigen compatibility with the potential  
833 recipient, GFR measures, imaging of the kidneys and the urinary tract, cardiac testing, and other tests  
834 depending on the medical history. This is because, the donor's short and long-term well-being after  
835 donation remains a first priorityPre-emptive transplantation (kidney transplantation before even  
836 initiating dialysis) may offer several benefits to ESKD patients but its impacts remain under  
837 evaluation <sup>200</sup>. The half-life of a transplanted kidney is <20 years, making these patients also potential  
838 candidates for CKD treatments during their life span <sup>201</sup>. For example, recurrent glomerulonephritis is  
839 an unpredictable complication that can have a negative impact on graft outcome <sup>202</sup>.

840

### **841 [H2]Conservative treatment/palliative care**

842 Kidney replacement therapy may not be available or affordable but it may also not be advisable for  
843 medical reasons. Especially in very old ESKD patients, dialysis may neither increase life span nor  
844 improve quality of life (QOL) <sup>203-205</sup>: in such cases palliative (trying to control the symptoms of uremia  
845 affecting QOL <sup>206</sup>) and education starting at CKD G4 (aimed at explaining comorbidity management)  
846 may be appropriate. Withdrawal from dialysis is a related issue and is common in very old  
847 hemodialysis patients <sup>207</sup>.

848848

## 849 [H1] Quality of life

850 CKD-related symptoms increase along CKD progresses and are key drivers of poor QOL in patients  
851 with CKD and ESRKD <sup>208-210</sup>. In contrast, symptoms rapidly improve upon kidney transplantation.  
852 Symptoms are most severe in dialysis patients, who frequently report fatigue, nausea, dyspnea,  
853 anorexia, pruritus, restless legs, and cramps <sup>211</sup>. Pain is especially common: in a survey of 205  
854 prevalent patients on hemodialysis, approximately 25% had “severe” pain during the 24h preceding  
855 the interview, and an additional 12% had “moderate pain” <sup>212</sup>. Mental illness including depression  
856 and anxiety are also common <sup>213</sup>, but are understudied among people with CKD. Unfortunately,  
857 clinical and epidemiological characteristics associated with the presence, severity, onset and  
858 remission of uremic symptoms are incompletely described; their pathophysiology is poorly  
859 understood; and few drugs have been approved by regulatory authorities for their treatment <sup>214</sup>.

860 Comorbidity and complications of CKD also substantially contribute to the reduced QOL in  
861 CKD patients. In some cases (e.g. anemia), effective treatments are available. In others, treatment is  
862 technically possible but has significant limitations, and treatment itself frequently causes additional  
863 symptoms and morbidity (e.g. dialytic management of hypervolemia). Despite the best efforts of  
864 clinicians, interactions between complications and their treatments can further compromise QOL for  
865 patients (e.g. volume overload resulting from sodium bicarbonate treatment of acidosis).  
866 Management of multiple comorbid conditions is already complex in patients with normal kidney  
867 function <sup>215</sup>; the situation is even more challenging in people with CKD, where the pathophysiology  
868 and optimal treatment of common coexisting conditions may differ from the general population (e.g.  
869 statins for coronary disease in dialysis patients). Lack of knowledge about how to prioritize and  
870 manage comorbid conditions undoubtedly contributes to the lower QOL in CKD patients through  
871 multiple mechanisms – including drug-drug and drug-condition interactions; pill burden; and  
872 decisional conflict for patients.

873 Dialysis is an effective life-support treatment but has many limitations in addition to those  
874 mentioned above. Key challenges for hemodialysis that specifically compromise QOL include poor

functional status (driven in part by procedure-related immobilisation, uremia-related malnutrition, and muscle wasting), the intrusive and time-consuming nature of the treatment, and vascular access infection and dysfunction <sup>216</sup>. Instruction for some home-based, low intensity physical exercise can improve physical performance and QOL in patients on hemodialysis <sup>217</sup>. Peritoneal dialysis also poses significant challenges for QOL including gastrointestinal distension, hernias, and chronic volume overload. Both forms of dialysis make employment difficult and both are associated with a high prevalence of infectious complications and undue pill burden. Some studies suggest that peritoneal dialysis is associated with slightly better QOL than hemodialysis <sup>218</sup>, but it is possible that this observation is confounded by patient characteristics <sup>219</sup>. Home dialysis strategies are constantly improving and are becoming possible tools to improve QOL <sup>220</sup>. Kidney transplantation is associated with substantially better QOL than either form of dialysis <sup>221</sup>, but even recipients with good graft function must face CKD-related symptoms as well as complications of immunosuppression and other treatments.

Recent emphasis on patient-centred research should help to improve QOL for people with CKD by increasing the likelihood that important but understudied issues such as symptom control are studied and new solutions are identified. In addition, findings from patient-centred research should help to drive uptake of patient-centred care at the bedside, especially if supported by patient-reported outcomes <sup>222</sup>. Such paradigm shifts should help to prioritize the management of patient-important issues such as reduced QOL.

## **[H1] Outlook**

There are many unmet medical needs in nephrology as a specialty and improving and refining our understanding of disease mechanisms in common and rarer conditions is lacking, as are novel therapies to treat rarer and common causes of kidney disease progression and a culture of curiosity and clinical trials that advance the field <sup>37</sup>. Key areas are to improve the identification of CKD and to reduce CKD risk factors, to improve the understanding of causes and consequences of CKD, to

901 improve outcomes with current knowledge, and finally to develop and test new therapeutic  
902 strategies <sup>37</sup>. Here, we highlight eight promising domains expected to produce significant impact on  
903 CKD management and outcomes.

904

## 905 [H2]How genetic kidney disease contributes to CKD

906 Genetic abnormalities were identified in 20% of CKD cases in children, adolescents, and young adults.  
907 Next generation sequencing have unveiled the extreme genetic heterogeneity of kidney disease. For  
908 example more than 40 different genes were discovered as possible causes of steroid-resistant  
909 nephrotic syndrome <sup>142</sup>. This requires implementation of current diagnostic strategies that go beyond  
910 th renal biopsy and open to personalized diagnosis and treatments <sup>142</sup>. In addition, first genetic  
911 modifiers of CKD progression such as *APOL1* or *UMOD* have been identified in older adults. CKD in  
912 adults may also relate to (genetically- or environmentally-defined) low nephron endowment or AKI  
913 episodes early in life, e.g. as early as during neonatal (intensive) care. Thus, CKD in adults, often  
914 classified by a single diagnosis, may often be the consequence of several components accumulating  
915 with time, a conclusion having important implications for the design of CKD trials, e.g. in prevalent  
916 entities such as “diabetic nephropathy”. Progress will require identifying the cause(s) of CKD and  
917 dissecting modifiable from non-modifiable drivers of CKD progression as well as specific  
918 pathophysiological mechanisms that might help to define more homogeneous patient subgroups.  
919 The identification of such subgroups is a prerequisite to conducting more targeted clinical trials,  
920 which require fewer participants and increase the possibility to identify appropriate drugs for  
921 different subtypes of patients. Patient heterogeneity is considered one of the main reasons why  
922 clinical trials in nephrology commonly fail <sup>223</sup>. Genetic investigations might therefore not only hold  
923 promise for individual patients, for example by facilitating the diagnosis of a monogenic disease with  
924 potential implications for individualized treatment, but might also improve classification and  
925 ultimately treatment and/or prevention in groups of patients <sup>224</sup>. The study of the genetic  
926 predisposition to kidney diseases has made major progress over the past decade. For the first time,

researchers have been able to carry out genome-wide screens to study complex kidney diseases, to which genetic susceptibility variants in many genes, as well as environmental factors, contribute. Genome-wide association studies (GWAS) have emerged as an important method to map risk loci for complex diseases by investigating the association of genetic markers across the genome with the disease of interest. We can predict that the list of genetic forms of CKD will exponentially increase together with our understanding of the genetic component of kidney function in health and disease<sup>224</sup>.

## **[H2]Biomarkers for CKD management**

As discussed, using serum creatinine-based diagnosis implies diagnosis as late as CKD G3, leaving a small window of opportunity for modulating CKD progression. Earlier identification CKD with biomarkers that can also predict CKD progression would help to initiate nephroprotective interventions<sup>37</sup>. Most attractive would be a marker of nephron number. Defining nephron number at birth would display low nephron endowment and help to dissect it from injury- or ageing-related nephron loss later in life. A marker of nephron number would detect CKD G2 and could serve as an end point parameter for clinical trials to quantify nephro-protective effects or drug toxicity. However, identifying a clinically applicable biomarker of nephron number in serum or urine has been unsuccessful so far. Biomarkers do not clearly discriminate nephron number from the compensatory increase in mass of remnant nephrons upon injury (remnant nephron hypertrophy). Imaging studies with tracers or the combination of imaging with kidney biopsy indicating the number of glomeruli and even SNGFR are promising as a proof-of-concept<sup>85, 225</sup>.

## **[H2]Separating triggers of nephron loss from CKD progression**

Congenital low nephron endowment, obesity, and AKI/CKD-related nephron loss imply hyperfiltration and hypertrophy of the remnant nephrons, which in turn promote secondary FSGS and further nephron loss. Interstitial fibrosis most likely represents matrix replacement of lost



nephrons, thereby stabilizing the remnant nephrons. Whether fibrosis itself contributes to nephron loss remains under debate and several antifibrotic drugs are under study to test this concept<sup>226, 227</sup>. Dissecting the relative contribution of nephron injury, wound healing, and compensatory hyperfiltration remains notoriously difficult in clinical practice. Finding ways to define their relative contribution and selectively target these mechanisms in a personalized manner remains a challenge for the following years.

## **[H2] Modifying CKD progression**

Among the many ideas on how to potentially modulate CKD progression some accumulated a large fundement of experimental evidence but still await successful validation in human RCTs (e.g. protecting nephron loss by modulating kidney fibrosis)<sup>228</sup>. In contrast, the idea to retard CKD progression with urate-lowering therapies already showed promising results in smaller trials and the results of ongoing multicenter RCT are eagerly awaited<sup>229</sup>. In contrast, the nuclear factor (erythroid-derived 2)-like (NRF)-2 agonist bardoxolone or folic acid supplementation have shown nephroprotective effects in RCTs in some populations but their mechanisms-of-action are not yet fully understood<sup>182, 230,231</sup>.

## **[H2]Nephrogenesis and regeneration**

Given the significant hurdles preventing widespread use of renal transplantation, Current work is exploring whether the transfer of autologous stem (progenitor) cells, stromal cells or other cell types can support the regeneration of injured nephrons (FIG. 8). For this to be a viable option, a growing research field is trying to unravel the physiology and pathophysiology of the nephron's intrinsic capacity to regenerate.

Several studies have identified possible drugable targets to specifically enhance nephron regeneration with pharmacologic intervention to prevent nephron loss in AKI and CKD<sup>232</sup>. In particular, targeting parietal epithelial cells that can act as progenitor for podocytes, to promote

their differentiation into fully functional podocytes and/or to block their excessive proliferation and matrix production can promote remission of glomerular disorders <sup>233-235</sup>. In addition, enhancing tubular regeneration by promoting tubular epithelial cell proliferation can reduce the occurrence of CKD after AKI <sup>234, 236</sup>. Although in vivo experimental studies appear promising, no clinical trials are available yet <sup>233-235</sup>. Finally, numerous Inhibitors of maladaptive repair induced improved tissue structure and even function in experimental models of CKD. Several phase 1-2 clinical trials were started but up to now, but none progressed beyond phase 2 <sup>237</sup>. However, other new antifibrotic drugs display are currently being tested in clinical trials <sup>234, 237,238</sup>.

Regenerative medicine is also being explored for treatment of kidney disorders. Therapeutic properties mesenchymal stroma cells (MSC), a population of well-characterized, easily obtainable cells with effective in numerous but not all experimental models of CKD <sup>239, 240</sup>. The underlying mechanisms of action of the MSC have been extensively described and consist essentially in immunomodulatory and paracrine effects. Similarly, numerous experimental studies reported improvement of kidney function and/or structure by using injection of human renal progenitors <sup>232-236</sup>. However, the translation of preclinical studies into robust, effective, and safe patient therapies remains limited <sup>233, 234,237</sup>.

Finally, the generation of 3D organ-buds termed 'organoids' from human induced pluripotent stem cells and embryonic stem cells was achieved also for the kidney; these organoids consist of a variety of renal cell types in vitro that mimic organs in vivo <sup>241, 242</sup>. The organoid bears great potential in the study of human diseases in vitro, especially when combined with CRISPR/Cas9-based genome-editing <sup>243, 244</sup>. However, the complexity of kidney structure and function is yet far from being reproduced for the purpose of clinical use for renal replacement therapy and the question if and when this will be eventually possible is still open.

## **[H2]Animal models and RCT design**

Innovative approaches to better link translational research to clinical trial findings will need to start with well-defined human genotypes and phenotypes to identify molecular targets, which may (or may not) subsequently be validated in animal models. Selecting such animal models for validation should be based on models that recapitulate CKD progression in humans and applying identical end points in subsequent clinical trials. This may include mice with identical pathogenic mutations as in human genetic kidney disease as being available for Alport syndrome, mouse models with a partial human immune system, or eventually experimentation in pigs or primates to close gaps between preclinical and clinical trials <sup>245, 246</sup>.

In addition, trial design may be improved upon reconsidering disease definitions, avoiding add-on designs using drugs with redundant mechanisms-of-action, preselecting patients with drug mechanisms-related biomarkers, and of study end points that better predict CKD progression to ESKD. For example, in order to test efficacy of the C5a receptor inhibitor avacopan in ANCA vasculitis the CLEAR trial at first avoided the usual add-on standard of care approach and compared instead avacopan plus low-dose steroids versus placebo plus high dose steroids on top of either cyclophosphamide or rituximab <sup>247</sup>. This way it was proven that avacopan is effective in replacing high-dose glucocorticoids in treating vasculitis.

## **[H2]Limiting cardiovascular morbidity and mortality**

Targeting the association of CKD with cardiovascular morbidity and mortality will require more functional studies in animals and humans to identify molecular targets potentially suitable for therapeutic interventions <sup>37</sup>. Controlling hyperlipidemia with PCSK9 inhibitors, suppressing systemic inflammation with innovative anti-inflammatory drugs, modulating the intestinal microbiota, or directly modulating vascular calcification and cardiac fibrosis may offer new solutions for this eminent problem in the future.

## **[H2]Translation of advances into daily practice**

The ever growing complexity of kidney biopsy reading, lab diagnostics, and the increasing need for genetic testing will require centers of excellence with sufficient resources to meet the diagnostic demands. The same may apply to upcoming costly therapies, where patient selection is of particular importance. Educational efforts are also needed to alert patients and general physicians to the increasing number of more affordable therapeutic options for CKD patients with diabetes, such as SGLT2 inhibitors. Finally, national CKD registries and treatment guidelines advocate awareness in the public, among health care providers, and decision takers, which can generate important support for implementation of standards <sup>37</sup>. Global guidelines created by the KDIGO initiative have become instrumental in this process starting from a global definition of CKD stages up to defining standards for the management of CKD complications (Box 3). In addition, global initiatives on CKD launched by the International Society of Nephrology define knowledge gaps in CKD and propose how to address them in the future <sup>37</sup>.

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1053 **Box 1. Risk factors for chronic kidney disease**

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- 1054 • Diabetes mellitus (type 1 or 2)
- 1055 • Poorly controlled arterial hypertension
- 1056 • Obesity
- 1057 • Monogenetic kidney disease (for example, autosomal dominant polycystic kidney disease,
- 1058 podocytopathies causing steroid-resistant nephrotic syndrome, Fabry's disease and Alport
- 1059 syndrome, complementopathies such as atypical haemolytic-uremic syndrome (aHUS)
- 1060 • Prolonged exposure to nephrotoxins (e.g., chemotherapy for cancer treatment, proton pump
- 1061 inhibitors, non-steroidal anti-inflammatory drugs, and anti-microbial agents), contaminated
- 1062 herbs, agricultural chemicals, heavy metals, irradiation)
- 1063 • Climate (excessive heat exposure and dehydration)
- 1064 • Infections and chronic inflammation (HIV, HCV, HBV, malaria, bacterial infections urinary

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tract infections, rheumatic disorders and autoimmune diseases)

- Low nephron endowment at birth (low birth weight, fetal dysmaturity)
- Obstructive uropathy
- Systemic vasculitis
- Hyperhomocysteinemia

- Malignancy (especially lymphocyte and plasma cell disorders such as multiple myeloma)

- Congenital renal abnormalities (CAKUT, vesico-ureteric reflux)

- Episodes of acute kidney injury

1077 **Box 2. Biochemical and serologic tests useful for defining causes of CKD**

1078 **[H1]Auto-immune disease**

- 1079 • Fluorescent anti-nuclear antibody, anti-dsDNA antibody, anti-phospholipaseA2 receptor
- 1080 antibody, anti-GBM antibody, anti-neutrophil cytoplasmic antibody, anti-phospholipid
- 1081 antibody
- 1082 • Serum hemolytic complement activity (C'H50), serum C3 and C4 levels, cryoimmunoglobulins

1083 **[H1]Malignancy**

- 1084 • Serum free light chains, serum or urinary immunofixation (multiple myeloma)
- 1085 • Serum albumin, phosphorous, total proteins and albumin/globulin ratio

1086 **[H1]Infections**

- 1087 • Human Immunodeficiency Virus, hepatitis B virus, hepatitis C virus serology, CD4+ T cell
- 1088 counts, urine, blood cultures, anti-streptococcal antibody tests

1089 **[H1]Monogenetic kidney disease**

- 1090 • Serum or urinary enzymes, glycolipids
- 1091 • Genetic testing using next generation and Sanger sequencing

1092

1093 **Box 3. Key strategies to managing CKD complications**

1094 **[H1]Renal anemia** <sup>187</sup>

- 1095 • Erythropoiesis stimulating agents (ESAs) are only given once all correctable causes of
- 1096 anemia (e.g. iron deficiency and inflammatory states) have been addressed
- 1097 • Adults received Iron supplementation when transferrin saturation is <30% and ferritin <500
- 1098 ng/ml; children (<18 years) receive Iron supplementation when transferrin saturation is
- 1099 <20% and ferritin <100 ng/ml
- 1100 • ESAs may be used to avoid hemoglobin <9.0 g/l with a target of max.11.5 g/dl
- 1101 • Avoid blood transfusion whenever possible, especially in potential transplant recipients.
- 1102 Caution in giving ESAs in people at risk of stroke or who have malignancy

1103 **[H1]Arterial hypertension** <sup>188</sup>

- 1104 • Individualize blood pressure (BP) targets are based on age and co-morbidities, with special
- 1105 recommendations for diabetes
- 1106 • Targets include normalizing body weight (BMI 20-25), NaCl intake (<5g/d), achieving regular
- 1107 physical exercise, limiting alcohol intake to 2 drinks/d (men), 1 drink/day (women)

1108 **[H1]Mineral and bone disorder** <sup>189, 248</sup>

- 1109 • Monitor calcium, phosphorus, parathyroid hormone, and alkaline phosphatase activity in
- 1110 adults beginning in CKD G3a and in children beginning in with CKD G2 ; 25(OH)D levels
- 1111 might also be measured and corrected by vitamin D supplementation as for the general
- 1112 population
- 1113 • In CKD G3a-G5D lower elevated phosphate levels toward the normal range but avoid
- 1114 hypercalcemia by restricting the dose of calcium-based phosphate binders
- 1115 • Avoid long-term exposure to aluminium in phosphate binders or dialysate
- 1116 • Measure bone mass density in patients with CKD G3a-G5D with evidence of bone disease to
- 1117 assess fracture risk if results will impact treatment In adults calcitriol and vitamin D



1118 analogues are no longer recommended for routine use unless secondary  
 1119 hyperparathyroidism in CKD G4-G5 is severe and progressive  
 1120 • For patients with CKD G5D PTH-lowering therapy calcimimetics, calcitriol, or vitamin D  
 1121 analogs are recommended  
 1122 • Consider patients with vascular calcifications at high risk for cardiovascular disease; avoid  
 1123 calcium-based phosphate binders in these patients, limit dietary phosphate intake.

1124 **[H1]Hyperlipidemia** <sup>249</sup>

1125 • Adults >50y with CKD should receive a statin; when eGFR <60ml/min, statin or  
 1126 statin/ezetimibe combination should be given  
 1127 • Adults <50y with CKD and other cardiovascular risk factors should receive a statin

1128 **[H1]Metabolic acidosis**

1129 • Oral bicarbonate can be used to correct mild metabolic acidosis

1130 **[H1]Chronic hyperkalemia**

1131 • Dietary restriction, loop diuretics, potassium-binding resins such as patiromer or dose

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**Figure legends**

**Figure 1. Kidney Disease Improving Global Outcomes (KDIGO) classification of chronic kidney disease (CKD).** The 2D matrix illustrates the predictive value of different levels of albuminuria and estimated glomerular filtration rate (eGFR). The color code indicates the risk for CKD progression to end-stage kidney disease (ESKD) and overall mortality. This matrix defines different stages of CKD referred as, for example, CKD G2A2 whereby the eGFR is 60-89 ml/min/1.73m<sup>2</sup> albuminuria is moderately increased; such a patient would have a moderately increased risk of progressing to ESKD. This staging system for CKD G2-G4 may underestimate the extent of irreversible nephron loss <sup>251</sup>. That is, if total GFR relies on the single nephron GFR (SNGFR) and the number of nephrons, SNGFR has to increase to compensate for reduced (or declining) number of nephrons to maintain total GFR. However, such a compensation may not occur with physiological ageing <sup>85</sup>. Additionally, total GFR drops if remnant nephrons are not able to increase SNGFR. Finally, increases in serum creatinine levels (representing a GFR of ≤40%) may imply remnant nephrons of ≤30% of a “normal” nephron number. Furthermore, the prognosis facet of CKD classification has been developed by large-scale population-based epidemiological studies, which suffer from a “false positive” rate of- approximately 30-35% as in such studies repeat analysis after 3 months was often not available <sup>43</sup>. Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1-150.

**Figure 2. Global prevalence of treated end-stage kidney disease per 1 million population.** The map depicts the prevalence of renal replacement therapy represented by kidney replacement therapy (kidney replacement therapy: hemodialysis, peritoneal dialysis, and kidney transplantation), for [Au:OK?ok] ESKD per 1 million population based on individual country data. Data not available indicates that data were either not known or not provided on the questionnaire for countries that

received the survey. Reprinted with permission from Bello, A. K. et al. Assessment of Global Kidney Health Care Status. JAMA 317, 1864-1881 (2017)

**Figure 3. Glomerular filtration rate (GFR) over time and impact of low birth weight on progression of CKD.** A. Population studies assessing estimated GFR document a decline in eGFR with age; here the data in men from Morocco are shown <sup>43</sup>. P values from P03-P97 represent the percentiles of the entire population with P50 representing mean values. This decline is a consequence of loss of functioning nephrons via glomerulosclerosis-related nephron atrophy and is not accompanied by a compensatory increase in SNGFR in the remaining intact nephrons, unlike what occurs when nephrons are lost by injury or surgery <sup>42, 52, 85</sup>. At age 70, nephron number is around 50% of that at age 25. Whether or not this implies increased SNGFR (single nephron hyperfiltration) of remnant nephrons or mirrors the declining demand for filtering metabolic waste is under debate but will strongly depend on co-morbidities such as obesity and the life time history of acute kidney injury episodes. In such cases, SNGFR should correlate with the total number of nephrons per body mass. B: Low birth weight (LBW) increases four-fold the relative risk to develop CKD by the age 17 as shown by population studies <sup>69</sup>. C: LBW status also significantly shortens the time span of when patients with IgA nephropathy reach end stage kidney disease <sup>70</sup>.

**Figure 4. Contributing factors to nephron loss.** In addition to ageing, acute and chronic forms of kidney injuries further may contribute to nephron loss along life time. Environmental, genetic causes and systemic disease-related reasons for low nephron endowment or causes of nephron injury are shown during the different phases in life, when they are most commonly (but not exclusively) encountered. Combinations of such causes determine the individual risk for CKD throughout life. For example, congenital abnormalities of the urinary tract (CAKUT) can lead to end stage kidney disease (ESKD) early in life, or to secondary focal segmental glomerulosclerosis (FSGS)-related ESKD later in life. Nephrotoxic drugs such as antibiotics, pain killers, contrast media for imaging or chemotherapy

can also influence risk, as can infections (bacterial, parasitic, viral). Severe genetic defects that lead to FSGS, Alport syndrome, cysts and atypical hemolytic uremic syndrome typically become evident early in life, whereas moderate genetic defects (such as mutation in *UMOD*) can become evident in adulthood. Genetic variants in genes such as *APOL1* can modify the course of diseases such as lupus nephritis.

**Figure 5. Injury, hyperfiltration and hypertrophy of the nephron.** A | In response to nephron loss, single nephron hyperfiltration induces an increase in nephron size as a compensatory mechanism to maintain overall renal function. Accordingly, podocytes need to undergo hypertrophy to maintain the filtration barrier of the increasing dimensions of the filtration surface. However, podocyte hypertrophy is limited; beyond a certain threshold, barrier dysfunction first manifests as mild to moderate proteinuria. At later stages the increasing podocyte shear stress promotes podocyte detachment. Parietal epithelial cells (PEC) host putative podocyte progenitors but proteinuria and potentially other factors inhibit their potential to replace lost podocytes and rather promote scar formation, i.e. focal segmental glomerulosclerosis (FSGS). B | Hyperfiltration and proteinuria both imply an increased reabsorption work load for proximal tubules. Activated tubular cells secrete pro-inflammatory mediators that promote interstitial inflammation. Together with the progression from FSGS to global glomerulosclerosis the inflammatory microenvironment of the tubulointerstitium promotes tubular atrophy and interstitial fibrosis. Scar formation is associated with vascular rarefaction and ischemia. The remnant nephrons have to further increase in size to meet the filtration demands, which accelerates the aforementioned mechanisms of CKD progression in a vicious circle.

**Figure 6. The earlier-the-better: renal outcome depending on when starting renin-angiotensin system (RAS) blockade in Alport Syndrome.** As shown, the time to renal replacement therapy was longest for those who started RAS inhibition early, at onset of microhematuria (usually at birth) or microalbuminuria (30-300 mg protein per day or per gram creatinine). Delaying until

macroproteinuria ( $>0.3\text{g/day}$  or per gram creatinine (green curve)) or CKD G3/4 has been established considerably shortens the time to renal replacement. Untreated patients (red curve) are relatives to Reprinted with permission from Gross, O. et al. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. *Kidney Int* 81, 494-501 (2012).

**Figure 7. Access for hemodialysis or peritoneal dialysis. A |** Arteriovenous fistulae are created by surgical anastomosis of a peripheral artery with a larger subcutaneous vein, e.g. at the forearm. The increased flow and perfusion pressure leads to structural modifications in the draining vein allowing repetitive venous puncture for hemodialysis. Sometimes declining blood flow to the hand and fingers (steal phenomenon), compensatory increases in cardiac output or aneurysm formation cause problems and require surgical correction. **B |** Arteriovenous grafts may become necessary when the patient's vascular status does not allow to build a fistula. Polytetrafluoroethylene grafts are mostly used and can be repetitively punctured for hemodialysis. Common problems are sterile inflammatory postimplantation syndromes or prosthetic graft infections causing bacterial sepsis. **C |** Central venous catheters become necessary when immediate initiation of renal replacement therapy is needed up to when a fistula or graft implant becomes ready for use. Such catheters may remain the last vascular access option for patients in which the vascular or cardiac status does not allow fistula or graft placement. Catheter infections or thrombotic complications remain constant concerns. Peritoneal dialysis requires placement of a transcutaneous catheter into the peritoneal cavity. This catheter allows fills, drains and refills of dialysate while the peritoneum serves as exchange membrane with the uremic blood. Fluid drains and refills with fresh dialysate are needed in regular intervals, usually 4 times a day.

**Figure 8. Targeting kidney regeneration.** In the future, it may be possible to target kidney regeneration and maladaptive repair to minimize the loss of injured nephrons and to protect the

remnant nephrons. Here, the most promising arenas of research include: 1. Enhancing podocyte regeneration. This aim may be achieved by drugs that promote differentiation into podocyte of parietal epithelial cell (PEC) progenitors of the Bowman's capsule and/or blocking their excessive proliferation. 2. Blocking fibrosis and/or maladaptive repair by inhibiting fibroblast expansion. 3. Enhancing tubular regeneration by blocking maladaptive repair and/or enhancing tubular cell proliferation<sup>233-238</sup>.

**Figure 9. Cell therapy and organoids as potential tools in CKD research and therapy.** (A) Injection of two cell types, mesenchymal stromal cells and renal progenitors, were reported as possible tools for cell therapy of CKD, improving kidney function and structure in animal models. Numerous phase 1-2 clinical trials are ongoing. Several mechanisms were proposed to explain the beneficial effects observed, mostly based on secretion of paracrine factors and/or microvesicles. For renal progenitors also direct engraftment in the injured tissue was reported. (B) Kidney organoids were generated in vitro starting from induced pluripotent stem cells (iPSC) and embryonic stem cells (ESC) and used for testing of drug toxicity and modeling of kidney diseases, with or without manipulation using Crispr/Cas and other genome editing strategies.

1272 **Table 1. Therapeutic interventions for selected conditions associated with CKD risk**

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| Disease entity                                      | Diagnostic test   | Therapeutic interventions  |
|---|---|--|
| <b><i>Genetic injury</i></b>                        |   |  |
| Polycystic kidney disease                           | Echography or MRI to detect cysts   | Tolvaptan (vasopressin receptor 2 antagonist of benefit in selected patients)  |
| Alport syndrome                                     | Genetic testing for collagen mutations  | ACE inhibitors to reduce filtration pressure in remnant nephrons   |
| Fabry disease                                       | Serum alpha-galactosidase activity  | Alpha-galactosidase replacement therapy  |
| Primary hyperoxaluria                               | Echography to detect nephrocalcinosis, urinary oxalate levels, genetic testing for serine—pyruvate aminotransferase , glyoxylate reductase/hydroxypyruvate reductase, and dihydrodipicolinate synthase-like | Increase fluid intake, supplementation with potassium citrate, magnesium oxide, pyridoxine , and orthophosphate, oxalate-reduced diet, liver transplantation |
| Cystinosis  | Leukocyte cystine levels, slit lamp exam of the eyes, genetic testing for the cystinosis gene   | Cysteamine substitution  |
| Coenzyme Q10-related gene mutations causing FSGS    | Genetic testing for AarF Domain Containing Kinase-4, coenzyme Q2, coenzyme Q6, and decaprenyl diphosphate synthase subunit 2  | Coenzyme Q10 replacement therapy   |
| C3 glomerulonephritis                               | Kidney biopsy, specific complement test, genetic testing for complement-related genes   | Plasma exchange or blood transfusion, rituximab, eculizumab (depending on specific cause)  |
| <b><i>Immune injury</i></b>                         |   |  |
| Acute or subacute immune complex glomerulonephritis | Autoantibodies against nuclear autoantigens or neutrophil cytoplasmic antigens such as proteinase 3 or myeloperoxidase,   | Immunosuppressive drugs, plasma exchange (in certain settings)   |



|  |   |   |
|--|---|---|
|  | C3/C4 serum levels urinary sediment, kidney biopsy                          |   |
| Renal vasculitis   | ANCA, urinary sediment, kidney biopsy                                       | Immunosuppressive drugs, plasma exchange (in certain settings)                  |
| <b><i>Vascular injury</i></b>                                    |   |   |
| Recent onset renal artery stenosis (fibromuscular or vasculitic) | Angiogram of the renal arteries   | Surgical revascularization or catheter-based angioplasty                        |
| <b><i>Metabolic injury</i></b>                                   |   |   |
| Diabetic kidney disease  | Blood glucose level, albuminuria, kidney biopsy                             | Antidiabetic drugs, SGLT2 blockade, RAS inhibitors                              |
| Chronic urate nephropathy  | Tophaceous gout, serum uric acid levels, kidney biopsy                      | Purine-reduced diet, uricosuric drugs, xanthine oxidase inhibitors, rasburicase |
| <b><i>Toxic injury</i></b>                                       |   |   |
| Toxic nephropathies (lead, aristolochic acid, phenacetin, ...)   | History, specific toxin levels, kidney biopsy                               | Abandon toxin exposure  |
| Multiple myeloma   | Serum or urinary free light chain test, bone marrow aspirate, kidney biopsy | Myeloma-directed chemotherapy   |
| <b><i>Kidney infections</i></b>                                  |   |   |
| Bacterial pyelonephritis   | Urine culture   | Increased fluid intake, antibiotics   |
| Viral nephropathies  | Viral testing, kidney biopsy  | Antiviral therapy   |
| <b><i>Mechanical injury</i></b>                                  |   |   |
| Obstructive nephropathy  | Renal ultrasound  | Relieve obstruction   |

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gure 2

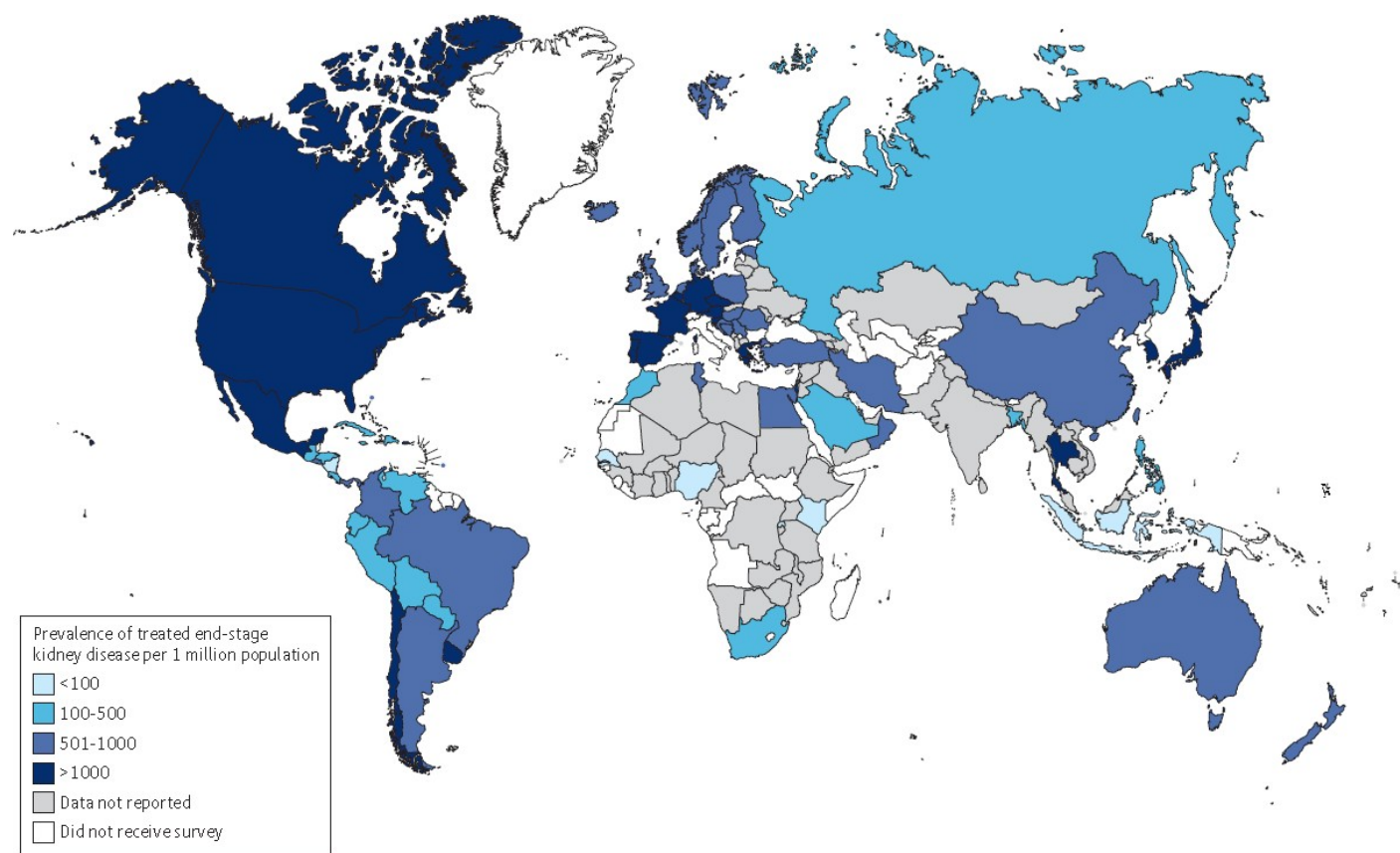


Figure 3

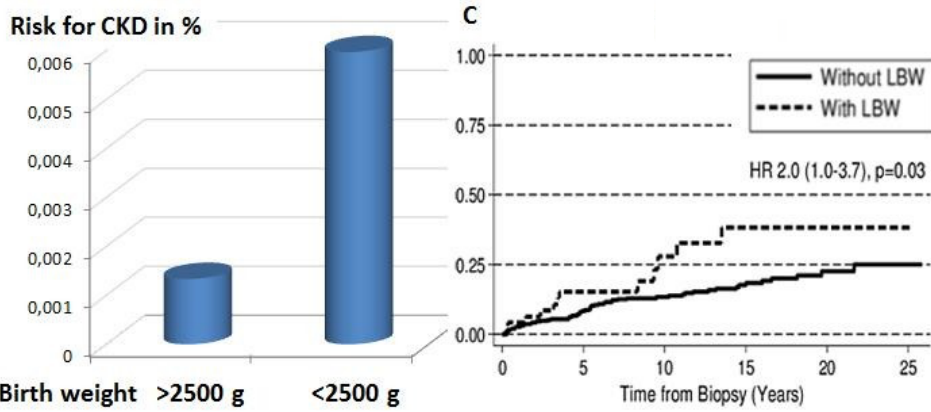
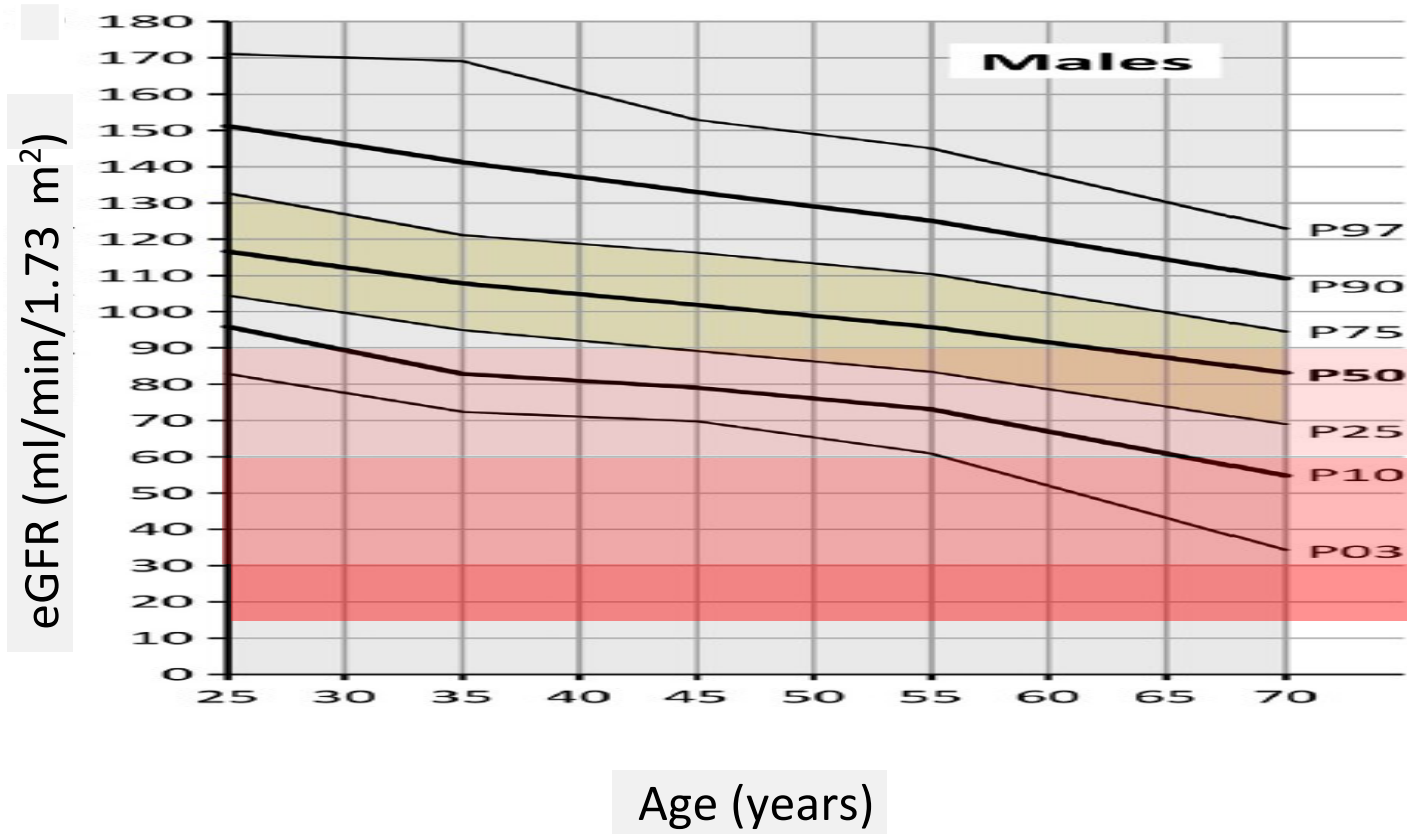
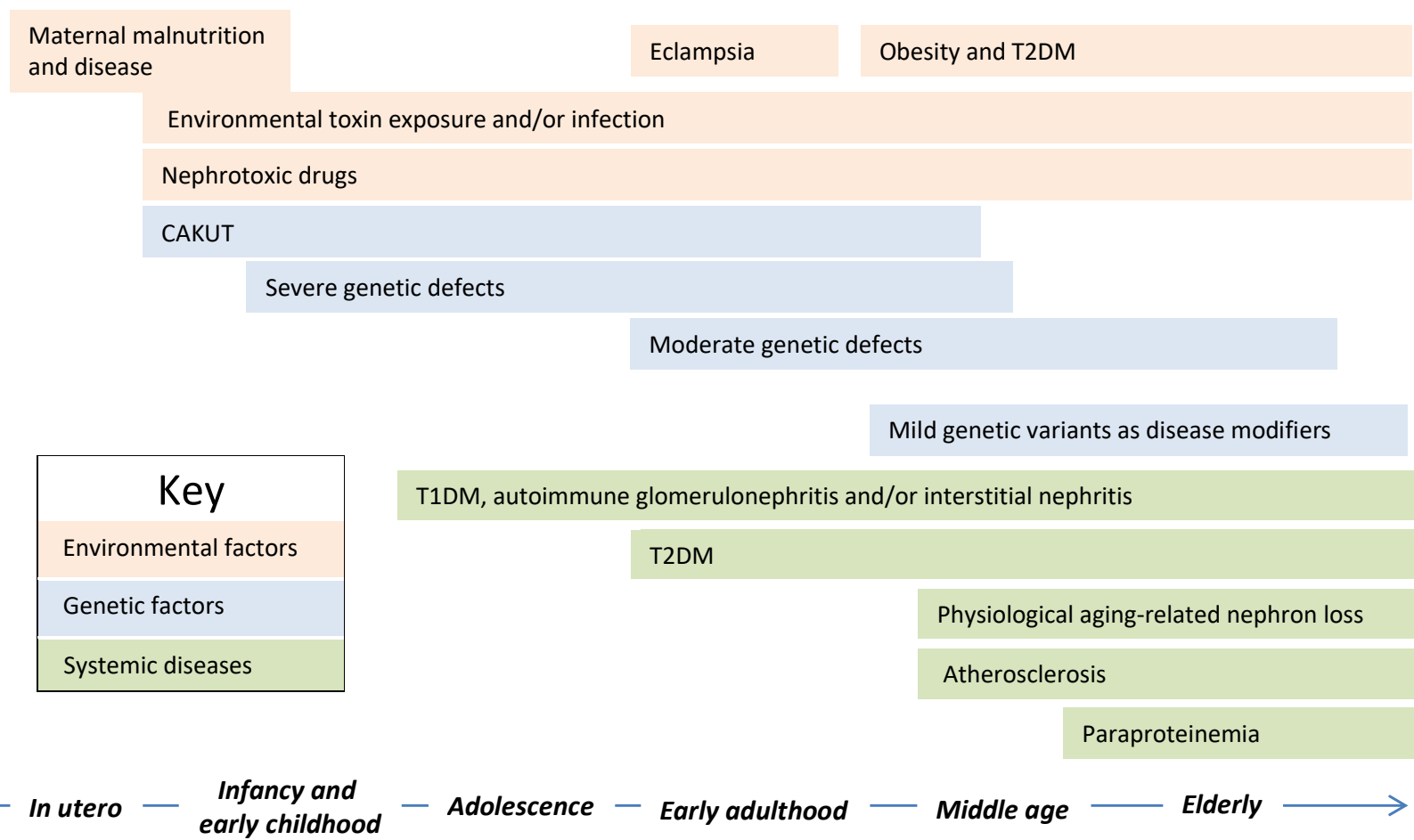
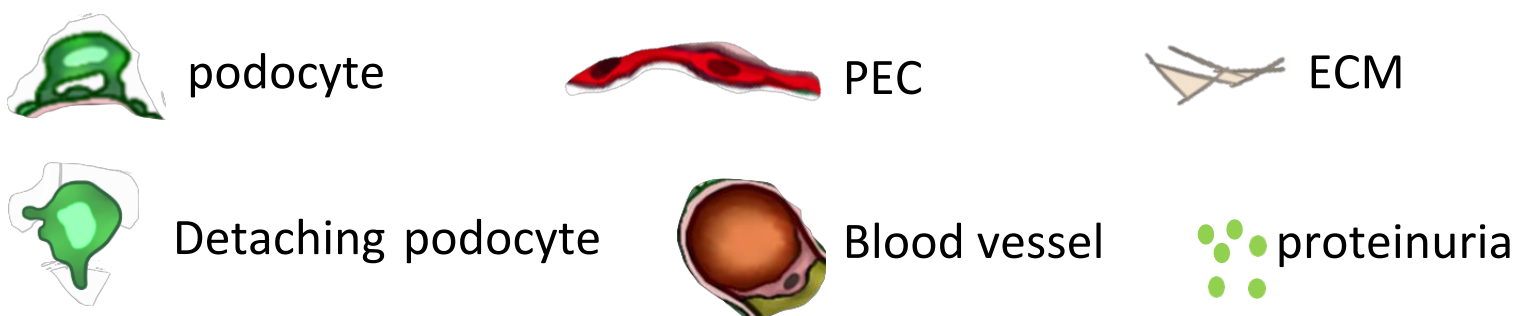
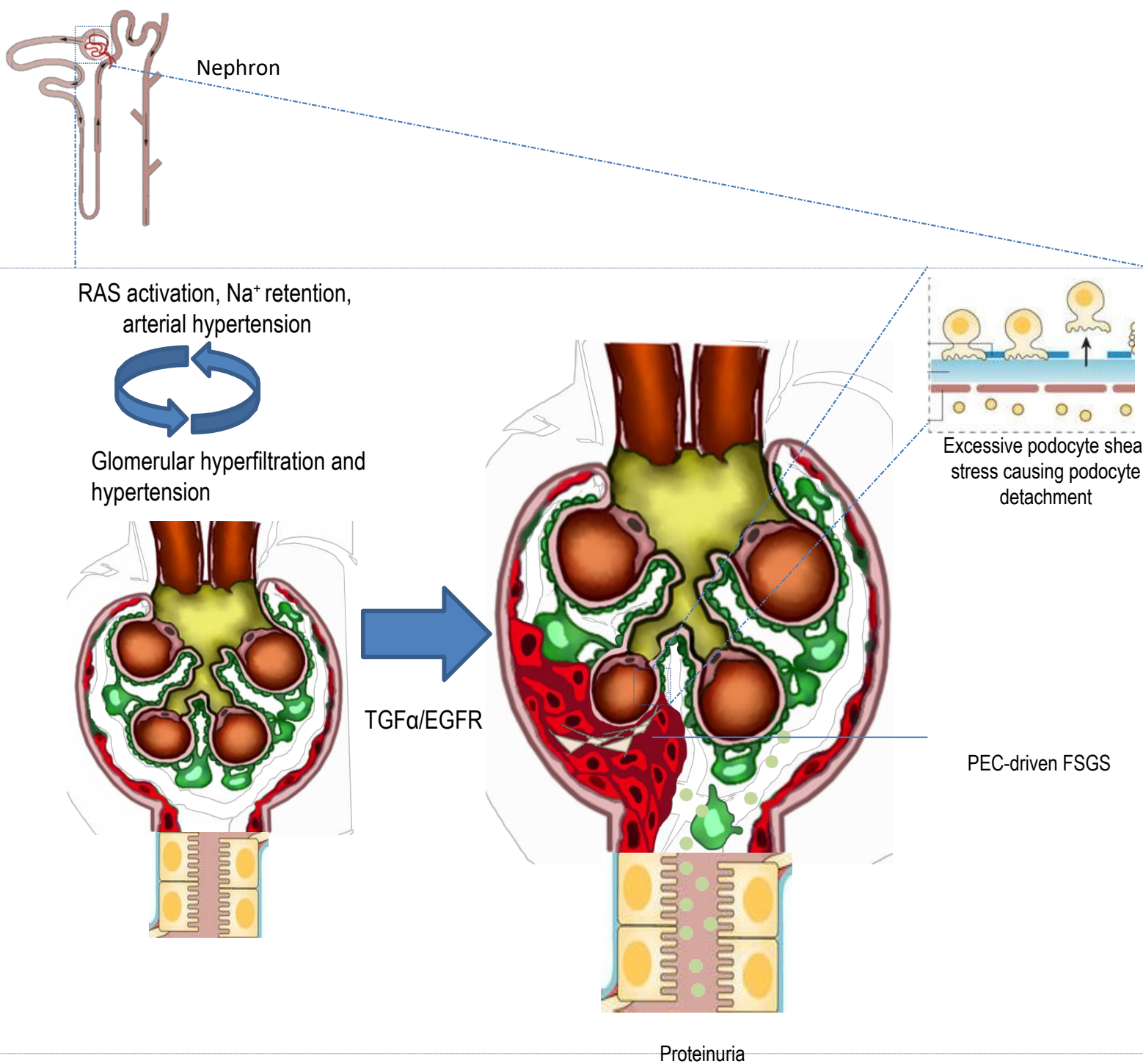


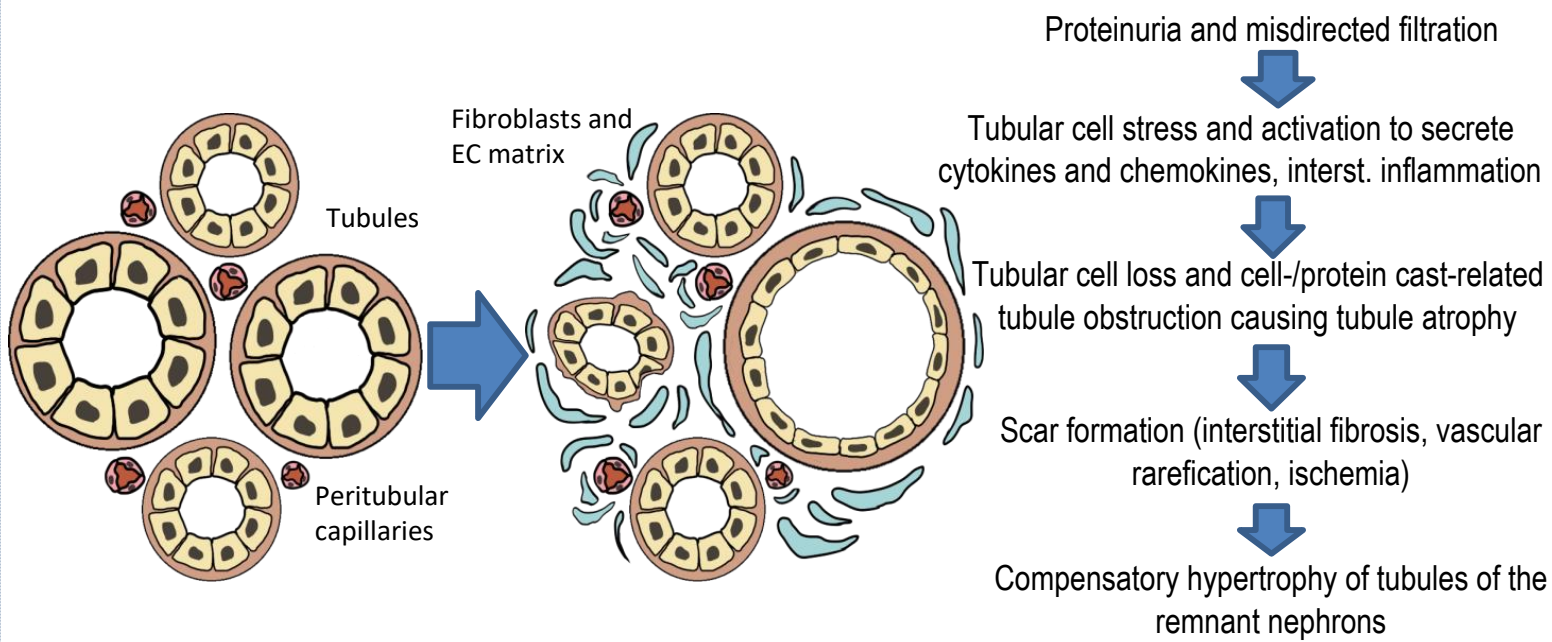
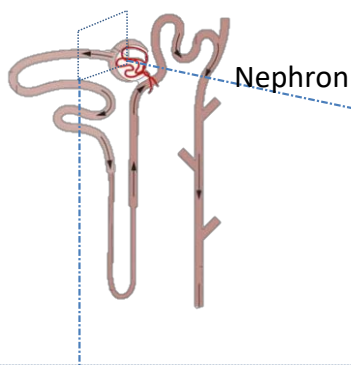
Figure 4



gure 5A



gure 5B



gure 6

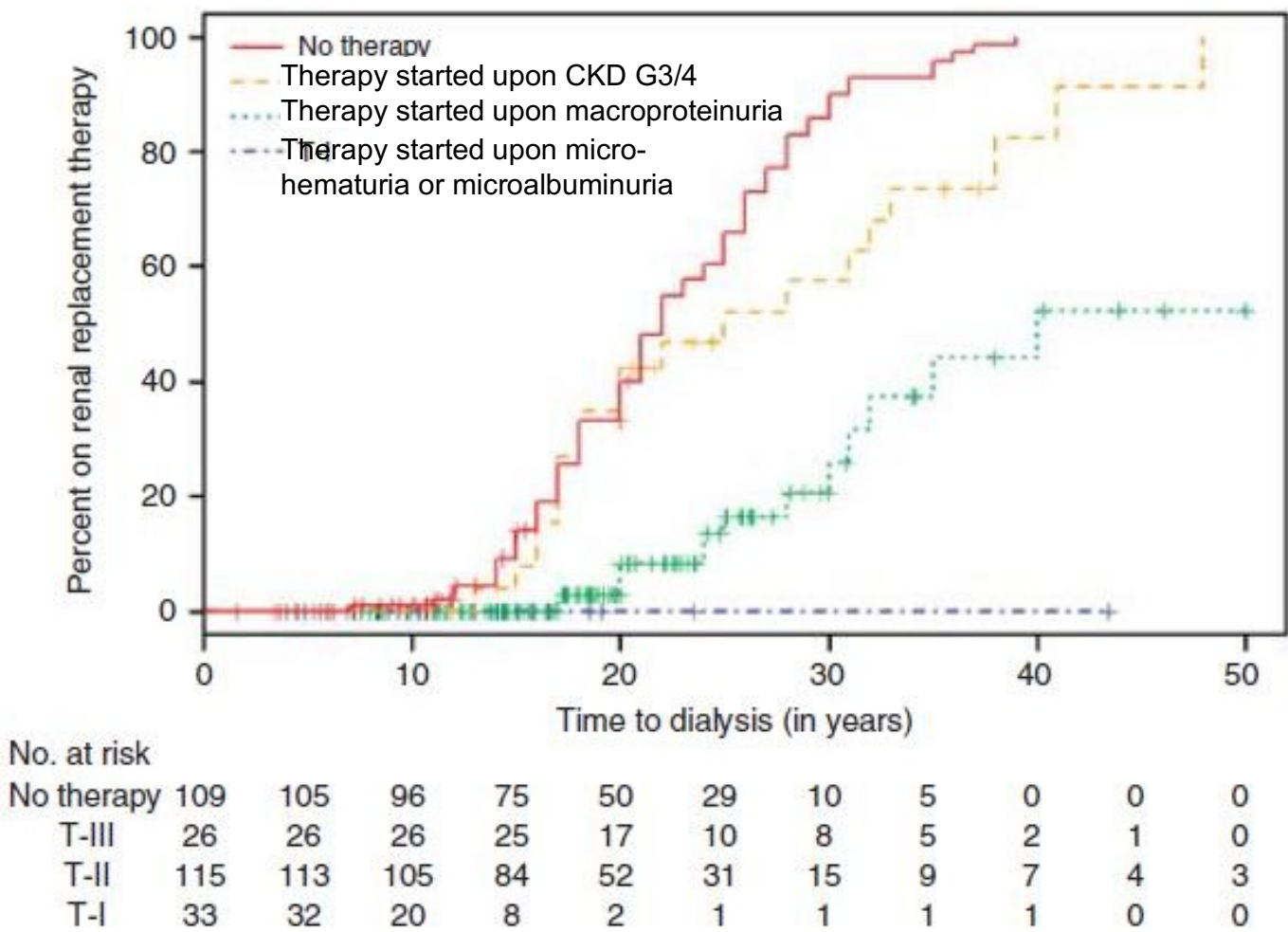
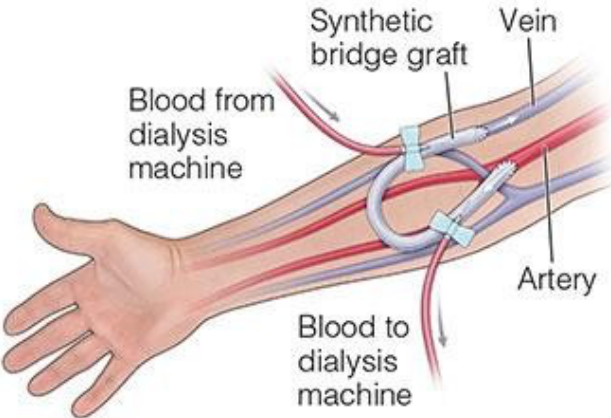
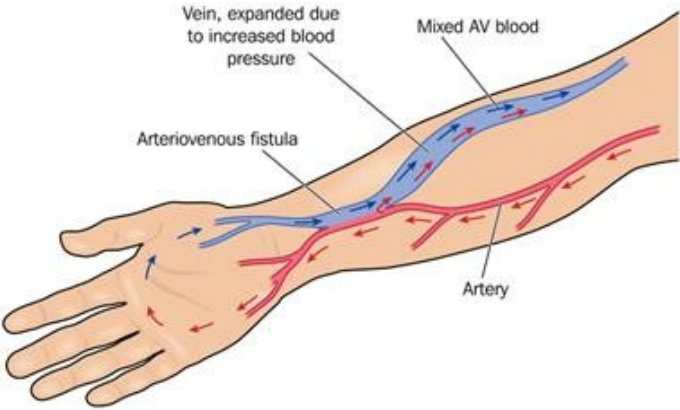
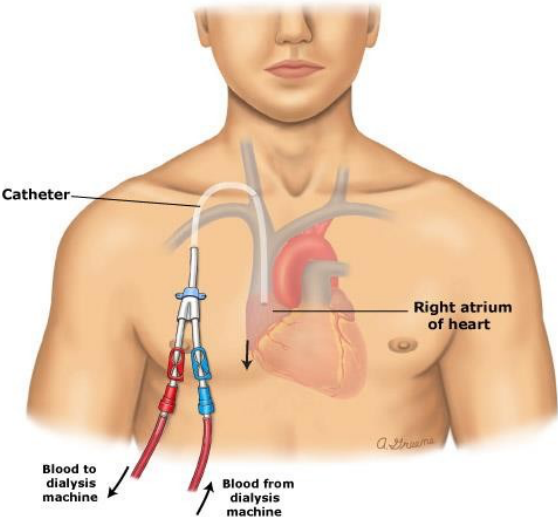




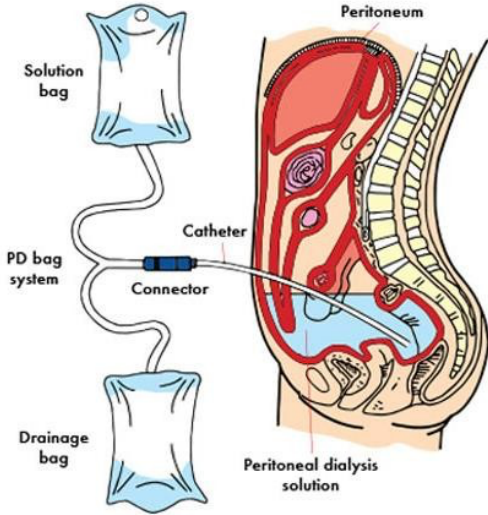
figure 7



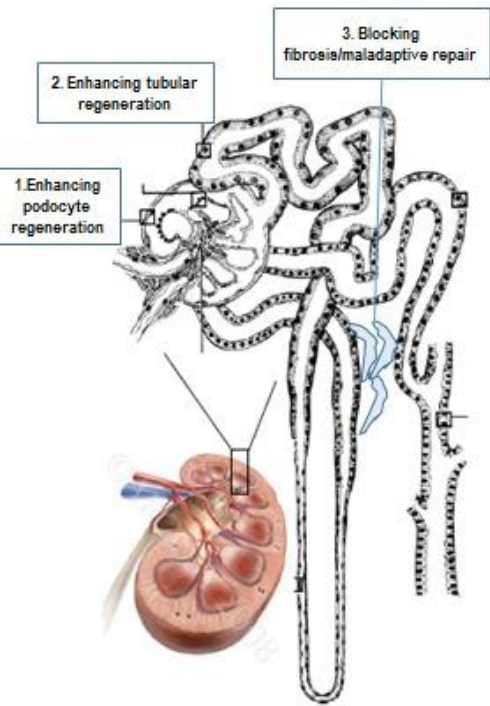
C



D



gure 8



**1A.Promoting PEC progenitor differentiation into podocytes:**



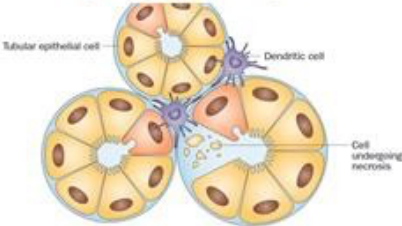
**1B.Blocking PEC progenitor overgrowth and matrix production**



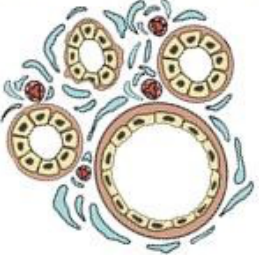
GSK3 inhibitors  
Retinoic acid  
miRNA 193a  
RAS inhibitors  
Leptin

SDF1 antagonists  
Steroids/Steroid receptor inhibitors  
Notch antagonists

**2. Promoting TEC proliferation**  
(IL-22, HDAC inhibitors)

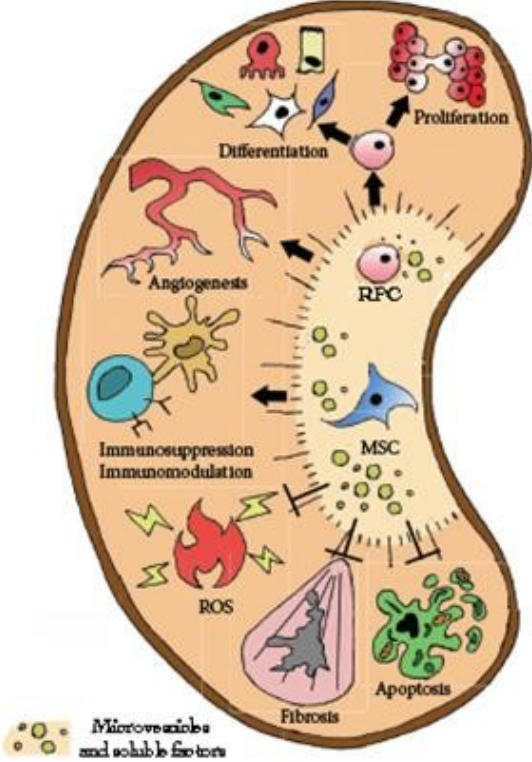


**3. Blocking fibrosis/maladaptive repair**  
Pirfenidone, GLI2 inhibitors, Galectin3 antagonists





A



B

